Obesity (A Growing Epidemic) – Preventive Measures and Drug Therapy

Pranav Kumar Yadav*[1], Rakesh Kumar Sharma[1] & Rajneesh Prasad[1]

[1]*Department of Analytical Research, Ayushraj Enterprises Pvt. Ltd., Gram Mansinghpura, Dehmi-Begus road, Ajmer Road, Jaipur-303007, Rajsthan, India*

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Corresponding Author:
Pranav Kumar Yadav
Email Id:
pranavkumar.yadav16@gmail.com

ABSTRACT

According to data from the World Health Organization (WHO), one billion adults that are approximately overweight currently exist in the world, of which three hundred million are obese. These numbers led to the finding that obesity appears as a major global epidemic, affecting countries in all stages of development. Obesity is an excess body weight due to fat deposition as compared to set standards of body weight. Obesity is considered as a drastic disease in the context that it poses many health consequences which interfere with the normal life of the individual. Though it is determined by a number of methods, but body mass index (BMI) has become the measurement of choice for many obesity researchers and health professionals. Despite the widespread problem of the obesity epidemic not many successful drug treatments are available in market for the prevention of obesity. This article provides a brief introduction and information, that is, measurement, trends, lethal consequences, etiology and available potential drug treatments for the obesity. Further, some plants are also mentioned that are prominently used in the dietary supplements which are claimed to posses anti-obesity effects.

1. INTRODUCTION

During the 20th century, the leading causes of death in developed countries shifted from infectious to chronic diseases. Chronic diseases (cardiovascular disease, cancer, diabetes, obesity) more commonly known as life style diseases, are now among the most prevalent, costly and preventable of all health problems.[1]

Overweight and obesity are problems across all geographic regions and all segments of the population. The health conditions of overweight and obesity are serious problems and rapidly increasing in both scope and severity. Rates of overweight and obesity had soared by 25 percent and 61 percent, respectively, since 1991. Obesity increases the risk of multiple medical conditions, many of which are associated with high morbidity and mortality, such as type 2 diabetes, hypertension, and coronary heart disease.[2]

1.1 Obesity

The term obesity implies to an excess of adipose tissue (fat tissue) but the meaning of excess is hard to define, since fat mass cannot be measured directly in humans. A number of indirect methods are available and have been used to estimate the extent of the body fat store. These include sophisticated techniques using ultrasound, computer assisted tomography, magnetic resonance imaging, bioelectrical impedance, etc., but none of these are really practical in the clinical setting. Underwater weighing is used by researchers and is based on the difference in density of the different body components.[3]

However, simpler and most popular method for estimation of body fatness can be derived from using the patient's body weight and height and comparing these values – estimation commonly known as ***Body Mass Index*** or ***(BMI)***. This useful index is obtained by dividing the body weight in kilograms (kg) by the height in meters (m) squared (wt/ht^2). BMI correlates with the body fatness and with the risk of obesity-related diseases. BMI varies with age in that a desirable BMI for people aged 19-20 is between 19-24, for people aged between 20-55 is 23-27 that for

people aged 55-64 is between 25 and 29.9, obesity is a BMI over 30.[3, 4]

Estimation of overweight and obesity by using BMI is simple, quick and inexpensive but does have limitations. One limitation is that very muscular people may fall into the overweight category when they are actually healthy and fit. Another limitation with using BMI is that people who have lost the muscle mass, such as elderly, may be in the "healthy weight" category, according to their BMI – when they actually have reduced nutrition reserves. BMI is therefore, useful as a general guideline to monitor trends in the population, but by itself is not diagnostic of an individual patient's health.[5]

1.2 Trends and prevalence of Obesity

Obesity is recognized as a growing problem. The American Obesity Association describes it as "a global epidemic", which is increasing at "an alarming rate". According to the World Health Organization, there are now more than one billion overweight adults world-wide, at least 300 million of them are obese.[5]

Prevalence has steadily increased over the years among genders, all ages, all racial ethnic groups, all educational levels and all smoking levels. Currently, one-fourth world population has been estimated to be clinically obese.[6] The epidemic shows an uptrend in data collected and compiled by National Centre for Health Statistics in surveys called National Health and Nutrition Examination Survey (NHANES). As reported in these surveys, prevalence of obesity increased slightly in the next two decades, i.e., 14.1 % in the NHANES I of 1971 to 1974 and 14.5 % in NHANES II of 1976 to 1980 and the epidemic might be spreading.[7] By NHANES III, completed in 1994, the prevalence of obesity had

increased by more than half, to 22.5 % of the population. By the end of the survey, some 55 % of the total population was officially considered overweight.[8, 9]

High prevalence of obesity is also reported in the Brazil, Uruguay and Trinidad, which shows that the obesity is not the privilege of the developed countries and may therefore, expected to be found even in the developing countries with large sections of society in the low socio-economic class.[10]

Obesity is strongly associated with several major health risk factors which include diabetes, high blood pressure, high cholesterol, asthma, cardiovascular diseases, arthritis and poor health status. Compared with adults with normal weights, adults with BMI of 40 or higher had an increased risk of these diseases. Due to increased risk of diseases, mortality rate is higher in obese adults. Life expectancy of moderately obese persons could be shortened by 2 to 5 years. While men between 20-30 years old with a BMI ≥ 45 could shorten their life expectancy by 13 years; white women in the same category could lose up to 8 years of life.[11]

1.3 Etiology of Obesity

Obesity is a chronic condition that develops as a result of a complex interaction between a person's genes and the environment characterized by long-term energy imbalance due to excessive caloric consumption, insufficient energy output [sedentary lifestyle, low resting metabolic rate (RMR)] or both. A person's appetite is a desire for particular type of food. If the quest of food is successful, feeling of satiety occurs. Each of these sensations are influenced by environmental and cultural factors as well as specific centers of the brain especially hypothalamus.[12]

The hypothalamus centre is sensitive to catecholamines and beta-adrenergic stimulation which inhibits eating behavior. This provides at least one rational for the anorexiants effects of amphetamines. Recent studies suggest that the hypothalamus senses energy storage through the actions of a peptide hormone, called leptin, released from adipocytes responsible for the feedback signal from adipose tissue to regulate food intake. With an increased in the amount of adipose mass, adipocytes release leptin in the blood, leptin on reaching the brain crosses Blood Brain Barrier by fascilated diffusion and occupies leptin receptor in the brain. Stimulation of leptin receptor in the hypothalamus results in the following actions

➢ Decreased production in the hypothalamus of appetite stimulator, such as neuropeptide Y.

➢ Increased production in the hypothalamus of substances such as Corticotrophic Releasing Hormone, that decreased food intake.

➢ Increased sympathetic nerve activity which in turn increased metabolic rate and energy expenditure.

➢ Decreased insulin secretion by pancreatic beta cells, hence decrease energy storage.

Thus, leptin may be an important means by which the adipose tissue signals the brain for optimum energy and food intake.[13, 14]

Still another potential regulatory process in the regulation of adipose tissue mass and obesity involves the enzyme lipoprotein lipase specially Adipose Tissue Lipoprotein Lipase (ATLPL) which is present in fat, muscle and liver. This enzyme hydrolyzes fatty acids from the triglyceride-rich lipoproteins and then these released fatty acids are taken up locally by adipocytes where they are converted to triglycerides and stored. The lipoprotein lipase hypothesis holds that in some obese states

excessive levels of this enzyme lead to preferential deposition of fat calories in adipose tissue inducing obesity.

Psychological, social and genetic factors also influence food intake. In many obese subjects these influence are over-riding; in general, obese patients usually response to external signals such as time of day, social settings and smell or taste of food to a greater extent than do normal persons. However, there may be the secondary reasons for the obesity which includes, Hypothyroidism - in which obesity can result because of decreased caloric needs, Insulinoma and Hyperinsulinemia can occasionally cause obesity, because of increased caloric intake secondary to recurrent hypoglycemia.[15]

1.4 Management of Obesity

Various approaches which can be used for management of obesity can be categorized into the non pharmacological and pharmacological approaches. Non pharmacological measures include regular exercise, combined with eating a healthy well-balanced diet and behavior modification. But these tactics are often unsuccessful on long term basis. When all other modes of losing weight have failed, pharmacological approaches (i.e., drug therapy) can be used to stimulate weight loss by either decreasing the appetite or inhibiting the absorption of fat from the intestine. Table 1 describes some of the commonly used drugs with their mechanism of action.[16] Table 2 describes some antiobesity drugs with their side-effects.

Despite the widespread problem of the obesity epidemic not many drugs are available in market for the treatment of obesity. Two products, Roche's Xenical (Orlistat) and Abbott's Reductil

or Meridia (Sibutramine), dominate the Anti-Obesity class.

Table 1- Commonly used drugs with mechanism of action [17]

Mechanism of action	Drug
Dopaminergic agonist	Phentermine, Diethylpropion
Noradrenergic and serotonergic re-uptake inhibitor	Sibutramine
Pancreatic lipase Inhibitor	Orlistat
Selective serotonin re-uptake inhibitors	Fluoxetine, Paroxetine, Fluvoxamine, Sertraline

Xenical is a lipase inhibitor that blocks the absorption of dietary fat in the intestines. It has some benign but unpleasant gastric side-effects, however, notably oily stools and urgency, which often prompt patients to discontinue treatment. There is low regulatory tolerance for side effects with obesity drugs, as they are given to otherwise healthy individuals; this sector has been a problematic one for pharmaceutical companies in the past, with all drugs apart from Roche's Xenical having been withdrawn at some point.[19]

Meridia (Sibutramine) is appetite suppressant which acts by stimulation of sympathetic nervous system.

Sibutramine is a β-phenethylamine that selectively inhibits the reuptake of noradrenaline, serotonin (5-HT) and, to a lesser extent, dopamine. Sibutramine's side-effects include dry mouth, headache, insomnia, constipation and increased blood pressure.[20]

Also, certain antidepressants such as Fenfluramine, Dexfenfluramine, Fluoxetine (Prozac) and Sertraline (Zoloft) may act on the

Table 2 – Commonly used drugs with their side effects [17, 18]

Trade Name	Active Molecule	Side Effects
Xenical, Alli	Orlistat	Steatorrhea, urgent bowel movements
Reductil, Meridia, Sibutrex	Sibutramine	Increases the risk of heart attacks and strokes in patients with a history of cardiovascular disease
Adipost, Plegine	Phendimetrazine	Allergic reaction, an irregular heartbeat, blurred vision, hallucinations, abnormal behavior
Aplenzin, Wellbutrin	Bupropion hydrobromide	Swelling of face, lips, tongue, or throat, seizure, severe blistering, peeling, swollen glands, and joint pain.
Desoxyn	Methamphetamine	Psychotic episodes, dizziness, dysphoria, euphoria, insomnia, urticaria.
Didrex	Benzphetamine	An irregular heartbeat, blurred vision, hallucinations, abnormal behavior.
Ionamin	Phentermine	Feeling short of breath, swelling, rapid weight gain, chest pain, fast or uneven heartbeat.
Pristiq	Desvenlafaxine	Nausea, Suicidal ideation, insomnia, hyperhidrosis, somnolence, delayed ejaculation.
Tenuate	Diethylpropion	Difficulty in sleeping, dry mouth, drowsiness, feelings of discomfort, feelings of elation, hair loss, hives, impotence.
Topiramate	Topiramate	Decreased sweating, flu-like symptoms, tingling of the skin, sore throat, severe allergic reactions blood in the urine, chest pain, decreased coordination, depression, memory problem, menstrual changes.

central nervous system and reduce food intake by enhancing satiety and increasing metabolic rate. But these were subsequently withdrawn from the market due to the development of cardiac valvular diseases.[18]

2. NEW PHARMACOLOGICAL APPROACHES

Newer drugs for obesity have begun to emerge and research is looking at different approaches, which lead to weight loss with fewer side-effects. Scientists have also been studying the interaction between fat and hunger. Fat produces a hormone called leptin, which turns off the feeling of hunger in the brain, so if we have high fat levels, our appetite is low. But when they drop we become hungry. Although, the link between leptin levels and hunger is not simple, it may be possible to develop drugs that interfere with this cycle. Amgen is currently studying metreleptin, a leptin analogue in clinical trials for obesity and diabetes.

A number of other obesity drugs are currently in clinical Phases (Table 3). Some are also being studied for other indications, often related to the concept of 'metabolic syndrome' (e.g., diabetes, hyperlipidaemia and obesity) [21]

Table 1.3 New Pharmacological Approaches for Obesity [23, 24]

Company	Drug	Phase	Mechanism of action
Arena pharmaceuticals	Lorcaserin (APD356)	III	Selective serotonin 2C receptor agonists
Alizyme's and Takeda	Cetilistat (ALT-962)	III	Lipase Inhibitor
Peptimmune	GT 389-255	I	Lipase Inhibitor
Novo Nordisk	'2-0453	II	An human protein analogue
Orexigen	Empatic (zonisamide sustained release (SR) and bupropion SR)	II	Sodium-channel modulation and enhancement of dopamine and serotonin neurotransmission
Gsk	1521498	I	Mu-opioid receptor inverse agonist
Genaera Corporation	Trodusquemine	I	Inhibit protein tyrosine phosphatase 1B (PTP-1B)
Neurogen	NGD-4715	I	Antagonist at the melanin concentrating hormone receptor-1 (MCHR1).
Gw pharmaceuticals	THCV	I	Cannabinoid component
7TM Pharma	TM38837	I	CB1 receptor antagonist
7TM Pharma	Obinepitide	I	The Y2 and the Y4 receptors agonist
Novo Nordisk	Liraglutide	III	Human GLP-1 analogue
Novo Nordisk	NN9161	I	An human protein analogue
Trans tech pharma	TTP435	II	Selective inhibitor of AgRP
Trans tech pharma	HPP404	I	Selective H3 receptor antagonist
Surface Logix , Inc	SLx-4090	III	Inhibitor of enterocytic microsomal triglyceride transfer protein (MTP)
Nisshin Seifun Group and kyorin Pharma	N-5984	III	Selective β3-AR agonist that reduces plasma glucose, insulinemia, TG and FFA, while increasing glucose tolerance
BiolActis	MPM-FB036	II	Prevents obesity through the Th17-pathway by negatively regulating the granulocyte-dependent response and thus preventing recruitment of immune cells like macrophages in adipose tissues
Obecure	Histalean	II	H3 receptor antagonist
Zydus Cadila	ZYO1	II	Cannabinoid CB1 antagonist

Aplenzin (Bupropion) is an antidepressant that enhances norepinephrine activity and weakly blocks dopamine reuptake. Currently bupropion is approved for depression and smoking cessation and is not approved as a weight-loss agent [22]

Topiramate (Topiramate) is a structurally and pharmacologically novel anticonvulsant agent that was approved in 1996 for treatment of epilepsy. Animal pharmacology studies relevant to weight loss have demonstrated that topiramate can increase energy expenditure and reduce food intake, resulting in decreased energy deposition.

These effects were associated with a selective loss of body fat and decreased levels of certain metabolic variables (e.g., leptin, insulin).[22]

2.1 Traditional Therapy

Many health food and supplement stores promote various "natural" or herbal products for weight loss. Table 4 contains some important formulations containing the one or more plant ingredient as their active constituents used for obesity and cholesterol. It is also found that the many plants are also claimed to have the beneficial effects on the secondary problems of obesity, that is, reduction in cholesterol, reduce blood sugar, improve joint inflammation, etc. Plants, which are commonly used in preparation of weight loss formulations: *Hoodia gordonii*, *Garcinia cambogia*, *Commiphora mukul*, *Coleus forskohlii*, *Citrus aurantium* (Bitter orange), Green Tea, Caffien, Yebra mate, etc.[25]

2.12 Hoodia gordonii

Hoodia gordonii, a plant though, looks like a cactus, is actually a "succulent" that grows in the high deserts of the Kalahari Desert region of South Africa. It contains a molecule that has similar effects on nerve cells as glucose and tricks the brain into the sensation of fullness. *Hoodia gordonii* is entirely natural and has no stimulant properties.[30]

2.13 Garcinia cambogia

Garcinia cambogia, a diminutive purple fruit is native to India and Southeast Asia. The rind of this pumpkin like fruit is rich in a substance called Hydroxycitric Acid (HCA). Studies show that HCA can curb appetite, reduce food intake and inhibit the production of fats and cholesterol. HCA exerts its anti-obesity effects through its inhibition of the enzyme ATP citrate lyase, playing a critical role in energy storage and affecting the appetite. HCA inhibits the process of fat storage by binding to ATP-citrate lyase to reduce the production of acetyl coenzyme A, which in turn reduces the body's production of fat and cholesterol and hence, suppresses appetite and induces weight loss.[31]

2.14 Guggulipid

Guggulipid or gum guggulu is a yellow gum oleoresin extracted from the stem of the *Commiphora mukul* tree, which is native to India. Guggulipid was traditionally used as a treatment for obesity, lipid-related disorders, arthritis, bronchitis etc. The active components of guggulipid are lipid-soluble steroids classified as guggulsterones Z and E. Guggulipid has positive effects which include reductions in hyperlipidemia, inhibition of platelet aggregation, anti-inflammatory and antioxidant effects. Pharmacological studies revealed that the pure guggulsterone isomers had pronounced hypolipidemic activity. Therefore, it is generally accepted that guggulsterone is the bioactive constituent in guggul and gugulipid responsible for the therapeutic effects.[32, 33]

2.15 Ephedrine

Many weight loss studies have been conducted on Ephedrine which showed that ephedrine increases fat burning functions and limits fat storage by stimulating the sympathetic nervous system and elevating circulating catecholamine levels. Catecholamines in turn stimulate receptors in adipocytes (fat cells), which results in increased lipolysis, decreased lipogenesis (fat storage) in fat cells and increased thermogenesis in brown adipose tissue and skeletal muscles [34, 35, 36]

Table 4- Herbal Formulations for Weight Loss [26, 27, 28 29]

Product name and Dosage form (Reference).	Uses and actions	Main Ingredients
Citrin Plus, Capsule	Regulate blood glucose and promote lean body mass	*Garcinia cambogia*, Niacin, Chromium polynicotinate.
Diet-metabo-7, Tablets	Weight loss	Yebra mate, Green tea leaves.
DIM Plex, Capsule	Control appetite	Citrus aurantium fruit, Green tea (*Camellia sinensis* extract).
Calotren, Capsule	Appetite suppression	Glucomanan, Aloe vera
Be-Slim, Tablet.	Dieting and weight loss	*Shilajit, Guggul, Boerhaavia, Triphala, Cardamom, Tribulus*

2.16 Tea

The effect of tea on body weight is generally attributed to its caffeine content. But some studies indicate that a class of antioxidant polyphenols, known as catechins, may act synergistically with caffeine to cause increased energy expenditure in both obese and lean individuals. Green tea is a nonoxidized, nonfermented tea and contains about 30% w/w catechins in the dry tea leaves. The major catechins, which are found in abundant proportion, are epigallocatechin gallate, epigallocatechin, epicatechin and epicatechin gallate. Other compounds obtainable in green tea are the flavonols (quercetin, kaempferol and rutin), caffeine, phenolic acids, theanine, and flavour compounds. Black tea contains mostly theaflavins and thearubigins, catchetin polymers formed during the fermentation process. Green tea and its extracts have been shown to increase energy expenditure and fat oxidation in the short term in both animals and humans. Also, green tea extract exhibits marked inhibition of digestive lipases *in vitro,* which is likely to reduce fat digestion in humans.[37]

2.17 Glabridin

Glabridin is the major flavonoid of licorice (*Glycyrrhiza glabra*). Human and animal studies have shown that glabridin from licorice flavonoids has a beneficial effect on body weight control. The results indicate that licorice flavonoids have abdominal fat-lowering and hypoglycemic effects, possibly mediated via activation of peroxisome proliferator-activated receptor-*γ* (PPAR-*γ*).[37]

3. CONCLUSION

If continue to grow at such an alarming rate, the obesity will be one of the most complicated diseases in the near future for all types of society. So, it is the right time to develop the more intensive research and precautionary measures to control the disease. It is also noticed that there is a scarcity of effective drug treatments for obesity; therefore there is great potential in the market of anti-obesity drugs. Moreover, obesity is a multifactorial disease, that is, it has many health consequences and hence it is preferable to have the drugs which are also helpful in treating the secondary problems in addition to obesity. For this purpose, plant derived drugs have the greater potential in the field of anti-obesity drugs because many plants are able to cure more than one consequences of the obesity. Hence, it is advisable to formulate plant derived ingredients as this may be highly profitable segment of pharma business / Industry.

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