

OBESITY: PATHOGENESIS AND EMERGING TARGETS FOR DRUG DEVELOPMENT

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ABSTRACT

Obesity leads to premature death and impairs quality of life. In general, weight loss is responsible and reduced the risk of cardiovascular disease that is associated with obesity. One of the recognized and well-establishment treatment options for weight loss, i.e., pharmacotherapy, where cardiovascular safety issues with some previous weight loss drugs raise concerns for newly approved pharmacotherapies. Previously, number of anti-obesity drugs that are already withdrawn from the market because of adverse side effects. In the present study, our group focused only on anti-obesity drugs that are currently under investigation and also understand its pathogenesis. Although lot of anti-obesity drugs are in the pipeline, the process for getting such type of drugs to be marketed has recently proven so difficult.

Keywords: Obesity, Pharmacotherapy, Risk factors, Complications, Drugs.

INTRODUCTION

One of the major global health problems, i.e., obesity, has been growing worldwide. Around 1.5 billion overweight and 500 million obese individuals were reported [1,2]. Hence, overweight and obesity are included as risk factor for causing major diseases, i.e., cardiovascular disease including diabetes and cancer [2-5]. In an effort to regulate the body weight pertaining to reduce the burden of this disease, i.e., obesity, scientists focused on neuropeptides and transmitters that are widely used in brain circuits and provide signals to endocrine and metabolic system [6]. Now-a-day, major target, i.e., brain circuits and tried to prepare or synthesize new pharmaceutical drugs that are beneficial for the treatment of obesity [6]. Recently, the Food and Drug Administration (FDA) approved two anti-obesity drugs (e.g., lorcaserin and Qsymia) pertaining to reduce the burden of cardiovascular disease [6-8]. Previous drugs related to obesity were rejected or removed because of various side effects observed in various cardiovascular organs [6-8]. In brain, variety of neuropeptides and transmitters that are present and performed various steps (i.e., initiation, termination, and choice) for energy uptake and these signals are received through endocrine factors and peripheral nerves [7-9]. These signals that are transmitted through various metabolic systems including endocrine system showed enormous potential for the development of weight loss drugs [7-9]. Previously, a number of drugs are approved, for example, amphetamines and sibutramine. Recently, newly approved drugs, i.e., lorcaserin, Qsymia, tesofensine, and contrave-targeted monoaminergic systems.

Generally, obesity is associated with number of chronic conditions such as heart failure, type 2 diabetes, coronary artery disease, and osteoarthritis. [10]. This disease is normally reported worldwide and almost all the countries are facing the problem of obesity and showed lot of variation within or outside the country. These variations are generally because of lifestyle and high-fat diets that are increased globally [10]. Changes in dietary content and physical activity are often the result of environmental and societal changes that are linked with development but lack of supported policies such as health, agriculture, environment, food processing, marketing, and education. According to the National Health and Nutrition Examination Survey in year 2011-2012, it showed that 33.9% population are overweight (age more than 20), 35.1% obese, and 6.4% are extremely obese. These calculations were done on

the basis of heights and weights of individual person and these studies were conducted in the US. In addition, overweight, obesity, and extreme obesity were classified [11] in the form of body mass index (BMI) which is expressed in kg/m². Normally, BMI (Fig. 1) should be in the range of overweight (25.0-29.9), obesity (≥30.0), and extreme obesity (≥40.0).

To reduce the burden, many medications were used and some of them were approved as anti-obesity drug but later on withdraw from the market [11] because of serious adverse effects. Some of them are:

- Fenfluramine and dexfenfluramine (heart valve damage; 1990’s)
- Phentermine, diethylpropion, and mazindol (2000’s)
- Selective cannabinoid 1 receptor blocker, i.e., rimonabant (2009, FDA never approved because of side effects, e.g., depression and anxiety).
- Sibutramine (2010; increased cardiovascular events and strokes)
- Bupropion/naltrexone combination, i.e., Contrave (2011; potential cardiovascular risks).

In addition, number of preventive measures also be taken for obesity and is generally reported in infants and young children. Most of the preventive strategies related to obesity [10] that are included, i.e., avoiding use of added sugar when feeding infants; appropriate micronutrients including fruits and vegetables are needed to promote the growth of children; and restriction of soft drinks. In contrast, apart from preventive measures of obesity, our group focused on various medications related to its risks, complications, and most importantly drugs that are available for the treatment of obesity including several newer treatments currently being investigated.

MECHANISM IN THE PATHOGENESIS OF OBESITY

There may be several mechanisms that are involved in the development of obesity which is generally associated with various dysfunctions. Generally, obesity is associated with:

- a. Enhancement in production of reactive oxygen species (ROS; limits the bioavailability of nitric oxide [NO] through diminished NO production and direct inactivation of NO by superoxide, O₂⁻) [12,13]
- b. In muscle and kidney, endothelial nitric oxide synthase expression and its activity are totally diminished in obesity resulting in blunted NO production [14]
- c. Intracellular insulin signaling transduction pathway is totally impaired [15]

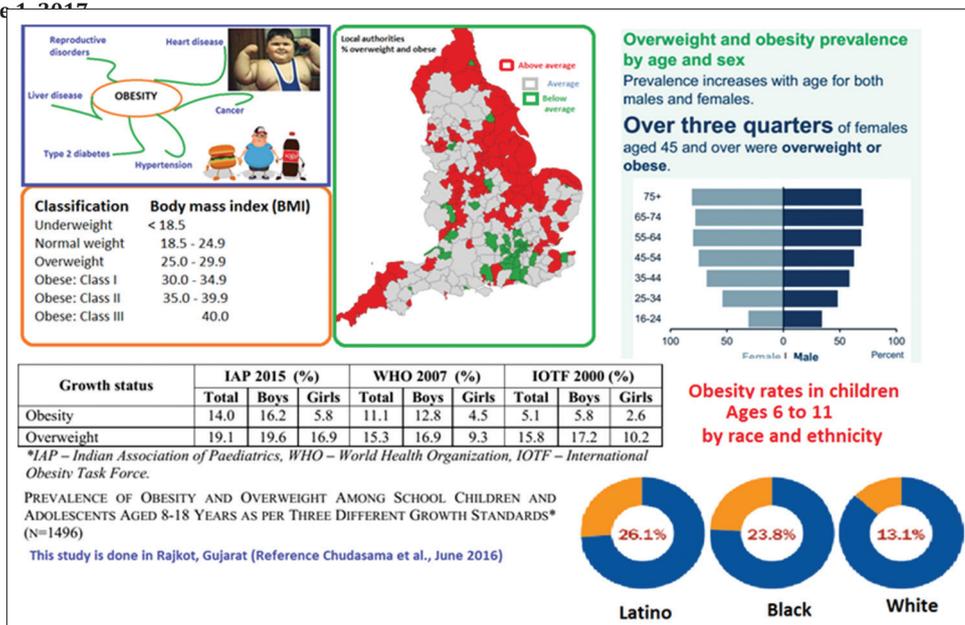


Fig. 1: Obesity and risk factors; overweight and obesity prevalence by age and sex; obesity rate in children (ages 6-11); and classification on the basis of body mass index including distribution rate in European countries. In addition, IAP, WHO, and IOTF data included for year 2000, 2007, and 2015 in Gujarat, India

d. Elevation in fatty acid induces phosphorylation of insulin receptor-mediated phosphorylation (IRS-1). These fatty acids tried to interfere with IRS-1 and in turn results in impaired activation of PI3-kinase [16].

In addition, adipose tissue not only functions as passive storage depot but also may be reported as a highly active endocrine organ. Adipose tissue including visceral adipocytes secretes a variety of immunologically bioactive molecules called adipokines. In case of obesity, there is an enhanced production of free fatty acids, angiotensinogen, leptin, resistin including several pro-inflammatory cytokines, i.e., tumor necrosis factor (TNF)- α and interleukin-6 (IL-6), whereas the production rate of adiponectin including anti-inflammatory adipokine is inhibited [17,18].

Among wide varieties of cytokines release by T-helper cells (Th1/Th2) or produced by adipose tissue, a more recent and less studied adipocytokine, i.e., anti-inflammatory cytokine IL-1 receptor antagonist (IL-1Ra). The key points of IL-1 Ra [19,20] are:

- Unprocessed or chemical free antagonist to the proinflammatory cytokine IL-1 and acts by binding to IL-1 receptors without inducing a cellular response
- Plasma IL-1Ra levels are elevated in human obesity and reduced after bariatric surgery
- Human adipose tissue appears to be a major source of plasma IL-1Ra and its expression in this tissue is markedly increased in obesity
- Plasma IL-1Ra levels are strongly correlated with insulin resistance.

We, therefore, explore the association between plasma elevation of IL-1Ra and abdominal adipose tissue depots measured by computed tomography. Our study revealed that circulating IL-1Ra concentrations were regulated or transformed to a greater extent by intra-abdominal than subcutaneous adiposity. We also found that plasma concentration of IL-1Ra levels increased with the number of metabolic abnormalities. Furthermore, scientists also reported and observe the association between IL-1Ra levels and several cardiometabolic risk variables which appeared to be partly independent from the variation in intra-abdominal adiposity.

In addition, cytokines, especially plasma TNF- α values, do not provide accurate information about the mechanism of action related to obesity.

sTNFR2 (soluble TNF receptor) is more stable protein as compared to sTNFR1, and therefore, it may be proposed that sTNFR2 should be a better diagnostic marker for TNF- α system activation in case of obese individuals with TNF-related insulin resistance [21,22]. Both the receptors of TNF- α are expressed in human adipose tissue and number of studies also claimed that TNFR2 could played a crucial role in the induction of insulin resistance. In other words, sTNFR2 levels are more closely related to abdominal adipose tissue accumulation and stronger independent marker of insulin resistance than TNF- α even after controlling for intra-abdominal adipose tissue [21-23].

EXAMPLES OF ANTI-OBESITY DRUGS THAT ARE CURRENTLY UNDER INVESTIGATION

Geographically, anti-obesity drugs' markets are present globally and these are segmented into North America, Europe, Asia Pacific, Latin America, and rest of the world. Recently, North America is number one shareholder for this market because of increased obese population. As per the reports of Centers for Disease Control and Prevention, more than one-third of the U.S population is reported in 2014 as obese. However, Asia Pacific is more expected to grow at much higher rate due to over demand of drugs and also increased its awareness related to risk associated with obesity. In addition, unhealthy diet would expect to enhance the number of obese people during forecast period. In this aspect, number of anti-obesity drugs that are currently under investigation:

Lorcaserin (approved in 2012; US FDA; Fig. 2), chemical entity that is able to activate serotonin 2C receptors in the brain. Because of this activation, these receptors are responsible for providing help and feel full after eating less quantity of food. The most common symptoms are observed in multiple Phase III clinical studies and are reported in both non-diabetic (headache, fatigue, nausea, dry mouth, and constipation) and diabetic (hypoglycemia, headache, back pain, cough, and fatigue) patients. This drug is called by different names, i.e., Belviq (US brand) and Venespri (Lorcaserin; Mexico brand) [24-26]. This drug is rapidly or quickly absorbed in gastrointestinal tract and is evenly distributed in central nervous system and cerebrospinal fluid. The major metabolite, i.e., lorcaserin sulfamate that is present in lorcaserin (70% plasma protein bound and metabolized in liver) and its excretion, is generally

through urine (92%) and minor excretion through feces. Most of the drugs that directly interfere with serotonin neurotransmission, i.e., selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitor, and monoamine oxidase inhibitors that generally lead to serotonin syndrome (symptoms such as increase in blood pressure, shivering, and sweating) [27,28]. In addition, this drug showed some enhancement in prolactin levels and is more contraindicated in case of pregnancy as weight loss cannot be able to monitor. This study is not reported and studied in patients below 18 years, so pediatric data are not available. Hence, no dose adjustment is required with mild to moderate renal and hepatic diseases [26-30].

- Phentermine and topiramate firstly approved by the FDA in year 2010; however, later on, this drug will reject because of adverse side effects such as heart beat rate increased, teratogenicity, and suicidality. Again in the year, i.e., 2010, the FDA wants additional data from Vivus (manufacturer) [9]. In 2012, again FDA recommended approval of phentermine and topiramate with some drastic changes from the previous ones and approved as a schedule intravenous drug under the brand name, Qsymia. This drug is more expected to treat number of obese patients (Basal metabolic rate, $BMI \geq 35 \text{ kg/m}^2$) or patients with obesity ($BMI \geq 30 \text{ kg/m}^2$) who have weight-related health problems, such as high blood pressure, type 2 diabetes, or abnormal levels of fat in the blood [31,32]. In Qsiva, the presence of two active substances and they are regarded as appetite suppressants. Functionally, phentermine suppresses appetite and is generally through chemical transmitter that are released and called

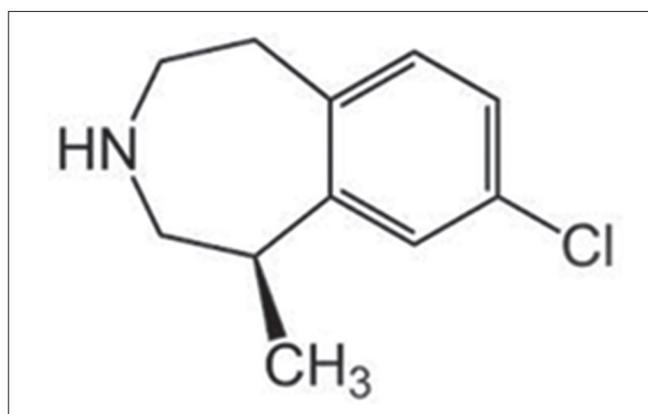


Fig. 2: Lorcaserin

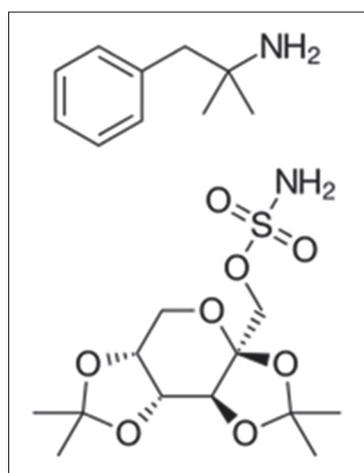


Fig. 3: Phentermine and topiramate

as norepinephrine (or noradrenaline) in the hypothalamus (region of the brain that controls hunger), whereas topiramate is thought to act by increasing the body's energy use, reducing energy efficiency, and reducing the patients' appetite for food. In addition to weight loss, phentermine and topiramate resulted in improved comorbidities and quality of life although not be able to shown or improve mental issues. Among the most common adverse events that are observed in clinical trials, i.e., paresthesia, dry mouth, constipation, and headache (Fig. 3) [31,32].

- Tesofensine (Fig. 4) is reported as anti-obesity drug and showed substantial weight loss in obese individuals. Drug development in the field of weight disorder has regularly faced pharmacovigilance hurdles [2,8,9] because anorexigenic drugs affect various systems (sympathetic, serotonergic, etc.) and thus lead or showed adverse reactions as well as the expected pharmacodynamic effect.
- Orlistat, gastrointestinal lipase inhibitor, approved by FDA in 1999; however, in year 2007, this drug withdraws from the market because of adverse effects [33]. Recently, cetilistat, novel, orally active, gastrointestinal, and pancreatic lipase inhibitor. *In vitro* studies claimed that cetilistat inhibited human pancreatic lipase with an IC50 in the low nanomolar range. In phase II, clinical trials in obese patients and also observed in obese patients along with Type 2 diabetes, cetilistat administered for 12 weeks significantly reduced body weight, serum low-density lipoprotein cholesterol, and total cholesterol in comparison to placebo (Fig. 5).
- In February 2016, Health Canada approved first new anti-obesity drug for Canadian in nearly two decades. Most of the Canadians are looking for medical treatment related to obesity and two prescription drugs are now available to them, i.e., first of them old anti-obesity drug, orlistat (Xenical; works by inhibiting fat digestion and reduced lot of calories absorbed from fat in the gut) and new one liraglutide

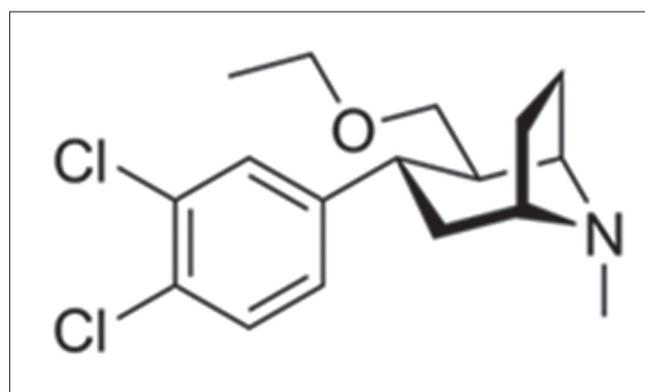


Fig. 4: Tesofensine

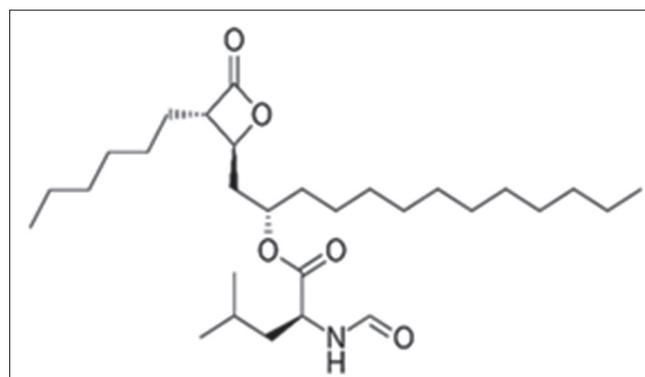


Fig. 5: Orlistat

(Saxenda; close analog to human glucagon-like peptide 1, gut hormone that played a key role in insulin secretion and appetite regulation).

CONCLUSION

Now-a-day, obesity has a rapid increment or enhancement leading to increased risk of various cardiovascular diseases (e.g., diabetes) and mortality ratio will increase year by year. In obesity, body weight is included under surrogate marker, but it cannot be able to predict the efficacy of drug samples clinically. Expectations from the researchers or scientists are more pertaining to anti-obesity drugs with no adverse effects after consuming. Till now, no anti-obesity agent has shown such type of clinical benefits but many anti-obesity drugs under development are the targeting of endogenous endocrine circuits regulating energy homeostasis. Overall, our group focused only on obesity and tried to support public health policy makers and practitioners. This paper provides some information about pathogenesis and provides available data related to anti-obesity drugs and evidence illustrate the prevalence trends in obesity and various cardiovascular diseases at a national and international level as well as the potential implications in terms of health consequences, inequalities, and cost.

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