1. INTRODUCTION

Chapter I

1. Introduction

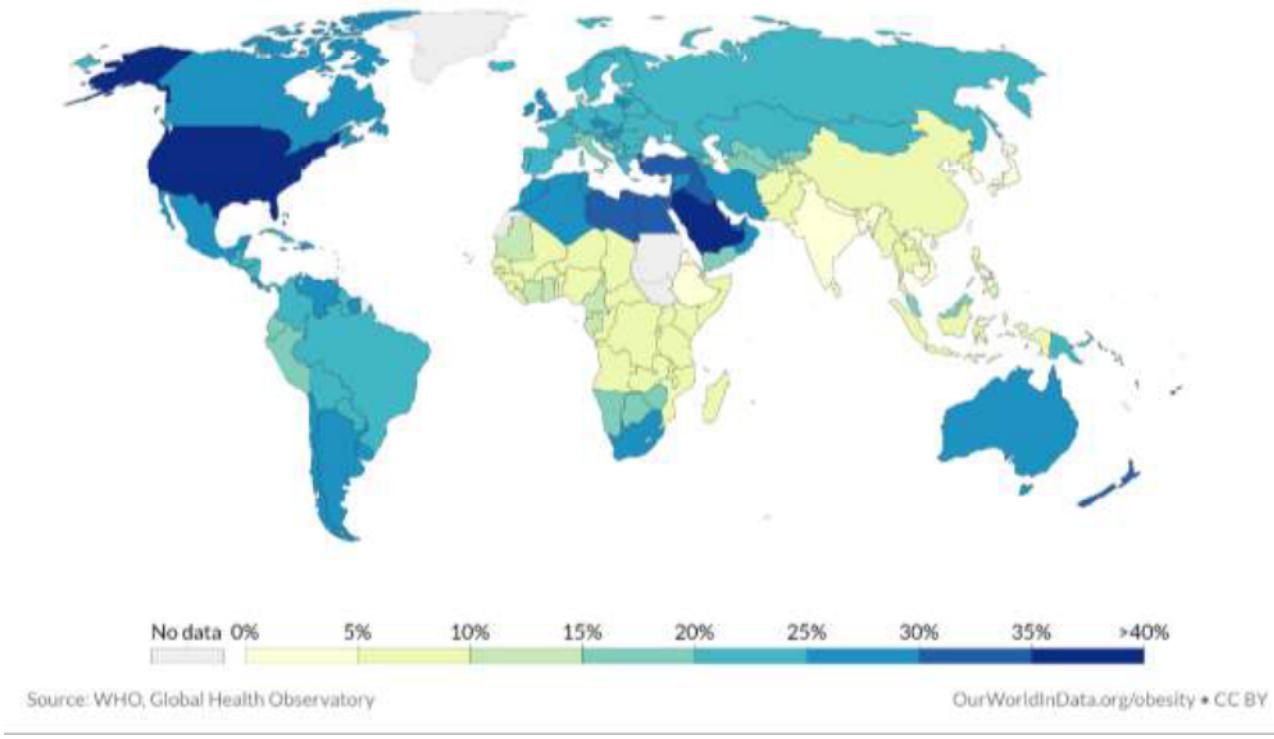
1.1. Obesity

1.1.1. Definition, Epidemiology

According to the World Health Organization (WHO), overweight and obesity are defined as "abnormal or excessive fat accumulation that presents a risk to health" [1]. However, the world obesity federation defines obesity as a "chronic relapsing disease process" [2]. The word obesity is derived from the Latin word *Obesitas* (*Ob* - over; *Esus* - Eating) means fat, stout, or plump. Obesity is associated with more than 200 disorders, that affects the entire human body [3]. Currently, numerous reports are available wherein obesity and its associated conditions worsen the outcomes of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4]. Though obesity is a preventable condition, in 2015, more than four million premature deaths were associated with overweightness and obesity [1,3].

Over the last century, obesity has emerged as a leading global pandemic through sedentary lifestyle associated with recent physiological, psychological, environmental, socio-economic and genetic factors [5]. Other than these factors, physical inactivity also plays a prominent role in development of obesity. It is reported that 3.2 million mortalities have happened due to physical inactivity across the globe. In 2016, around 1.9 billion people were identified as overweight, wherein 650 million people fell under the category of obese. The prevalence of obesity has tripled during 1975 to 2016 (**Fig. 1.1**). More people are reported to be obese than underweight and malnourished across globe, excluding sub-Saharan Africa and Asia continents. Children's obesity is also increasing drastically, where the affected children mainly belong to the developing countries, posing an additional health burden for the futuristic world. Approximately 10-fold increment in childhood and adolescence obesity was reported during the last four decades [1].

In the Indian scenario, obesity and overweight prevalence is growing faster than the world average. More than 135 million Indians are affected by obesity condition. According to ICMR-INDIAB study 2015, the prevalence rate of obesity varies from 11.8% to 31.3% [6]. S. Luhar *et al.*, forecasted that the prevalence of obesity in India will triple from 2010 to 2040 [7].



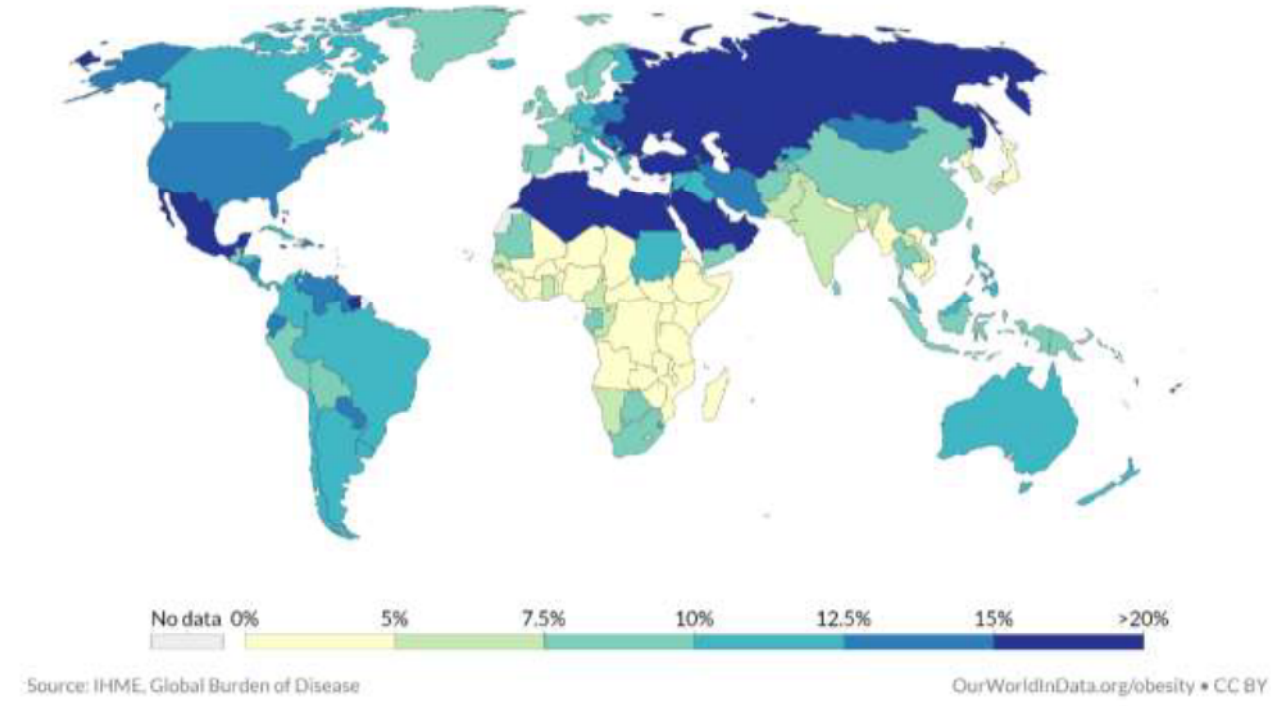


Fig. 1.1. Share of obese adults in 2016 (A) and share of obese associated deaths in 2017 (B)
Adapted from [8] with permission

1.1.2. Classification

Overweight and obesity are preliminarily classified (**Table 1.1**) using the Body Mass Index (BMI) and is calculated using the formula 1.1

$$BMI = \frac{Weight\ of\ the\ individual\ (kg)}{Square\ of\ the\ height\ of\ the\ indiviual\ (m^2)} \quad \text{.....Formula 1.1}$$

On the basis of BMI, an individual with BMI between 25-29.9 Kg/m^2 is considered overweight, while a BMI greater than 30 Kg/m^2 is obese.

Table 1.1. Summary of BMI based classification for overweight and obesity in different age groups.

	Adults (>19 years)	Children (5-19 years)	Children (< 5 years)
Overweight	25-29.9 Kg/m^2	BMI-for-age >1 standard deviation above the WHO Growth Reference Median	BMI-for-age >2 standard deviations above WHO Growth Reference Median
Obese	30-34.9 Kg/m^2 (Class I) 35-39.9 Kg/m^2 (Class II) ≥ 40 Kg/m^2 (Class III)	BMI-for-age >2 standard deviations above WHO Growth Reference Median	BMI-for-age >3 standard deviations above WHO Growth Reference Median

The diagnosis of obesity is currently based only on BMI, without an indication of the impact of excess adiposity on health. Sometimes, the BMI approach also lacks sensitivity towards individuals. To overcome these problems, numerous methods have been suggested.

Waist-Hip Ratio (WHR) is another parameter used to determine obesity and is considered more accurate in comparison to BMI. The WHO STEPwise approach to Surveillance (STEPS) provides a simple standardized protocol for measuring waist and hip circumference, which states that:

▪ The measurement of waist circumference must be made at the top of the iliac crest

▪ The measurement of hip circumference must be made at the widest portion of the buttocks. A WHR greater than 0.85 (for women) and 1.00 (for men) are considered obese [9].

Recently, W. Timothy Garvey and Jeffrey I. Mechanic proposed adiposity-based chronic disease (ABCD) classifications (**Fig. 1.2**). This coding system is mainly based on four domains namely: pathophysiology (A), BMI classification (B), specific biomechanical and cardiovascular complications remediable by weight loss (C), and degree of the severity of complications (D) [10].

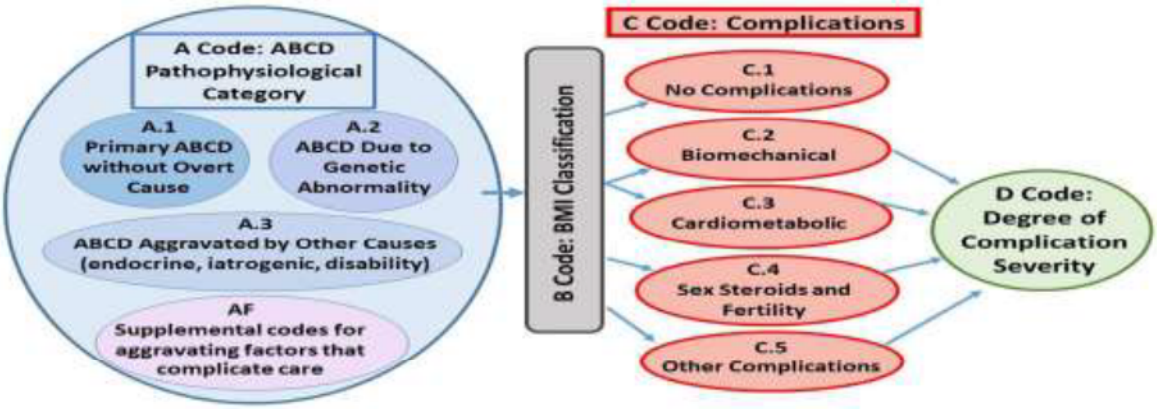


Fig. 1.2. Structure of the proposed ABCD systems. Adapted from [10] with permission

1.1.3. Treatment for obesity

The treatment of obesity is mainly focused to target both weight-related complications and adiposity to improve overall health and quality of life. Numerous treatment guidelines are available for the treatment of obesity. However, mainly three approaches namely lifestyle modification, pharmacotherapy and bariatric surgery are used. Lifestyle therapies individually results in 5 to 8% weight reduction, while pharmacotherapy results in 3 to 11 % weight loss. Bariatric surgery provides a weight loss of 14 to 43 % [5] and is recommended only to patients with BMI $\geq$ 40 kg/m^2 or BMI $\geq$ 35 kg/m^2 with comorbidities [11]. Thus, a combination of lifestyle modification and pharmacotherapy is suggested for the management of obesity.

Currently, there are six major FDA-approved anti-obesity medications (**Table 1.2**, **Fig. 1.3**). Except orlistat, remaining all drugs act through CNS pathways that either reduce appetite or enhance satiety. Orlistat exerts its activity by reducing fat digestion and absorption. Most of these anti-obesity drugs have an efficacy of 3 – 11 % (estimated net weight loss) [3,12]. Further numerous drug candidates focussing on a variety of targets are under clinical development program and are summarised in **Table 1.3**.

Table 1.2. Currently approved anti-obesity medications

Drug (dosage)	Mechanism of action	Administration	Common adverse effects	Clinical Trial and Duration	Weight Loss (%)
Phentermine (8 mg (short-acting), 15 mg, 37.5 mg)	Sympathomimetic amine	15 mg or 37.5 mg orally once daily; 8 mg orally 2–3 times daily; can start with a quarter or a half of a 37.5 mg tablet once daily and titrate upwards to a maximum dosage of 37.5 mg	Increase in HR and/or BP, dizziness, dry mouth, constipation, insomnia and irritability.	Aronne LJ, *et al* 28 weeks [13]	5.45 to 6.06
Orlistat (60 mg OTC, 120 mg)	Pancreatic and gastric lipase inhibitor	120 mg orally three times daily	Flatulence, bloating and diarrhea.	XENDOS 208 weeks [14]	2.71 to 9.6
Phentermine/ topiramate ER (3.75/23 mg, 7.5/46 mg, 11.25/69 mg and 15/92 mg)	Combination of sympathomimetic amine, anorectic and ER antiepileptic drug	Start with 3.75/23 mg orally once daily for 14 days; increase to 7/46 mg once daily and monthly titration upwards to achieve weight loss; discontinue if <3% weight loss on 11.25/69 mg or <5% weight loss on a maximum dose of 15/92 mg after 12 weeks	Peripheral neuropathy (usually transient), dyspepsia, insomnia, constipation and dry mouth	EQUIP21 56 weeks [15]	5.1 to 10.9
Naltrexone SR (8 mg)/ bupropion SR (90 mg)	Combination opioid antagonist and aminoketone antidepressant	Upwards titration over 4 weeks to a maximum of two tablets twice daily	Nausea, constipation, headache, vomiting, dizziness, dry mouth and diarrhea	COR-I 56 weeks [17]	5.0 to 6.1
Liraglutide (3.0 mg)	GLP1 receptor agonist	Start with 0.6 mg subcutaneously once daily for 7 days; titrate upwards weekly to 1.2 mg, 2.4 mg, and then the maximum dosage of 3.0 mg once daily	Nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, abdominal pain, fatigue, dizziness, increase in lipase levels and suicidal behavior or ideation	SCALE Obesity and Prediabetes 56 weeks [18]	8.0

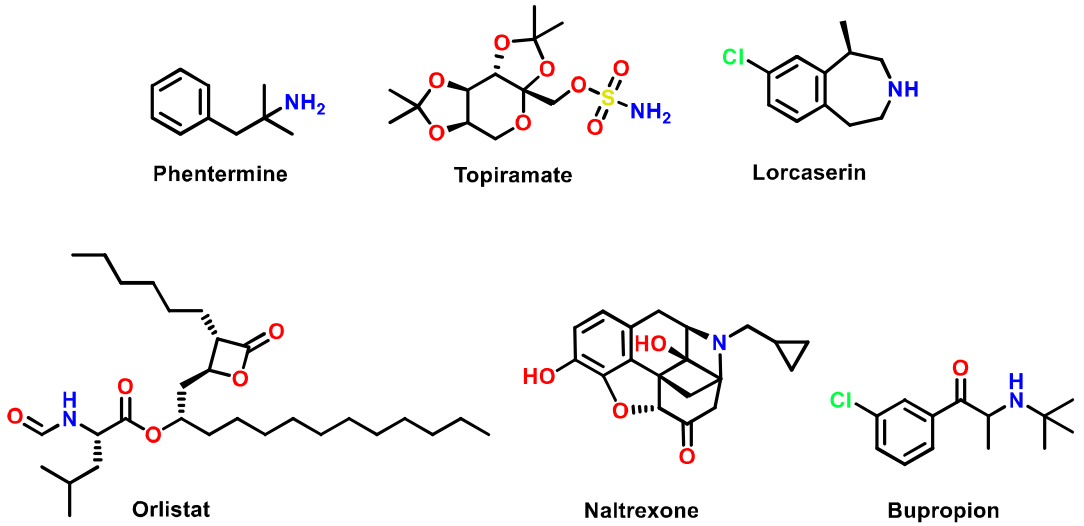


Fig. 1.3. Structures of approved drugs for the treatment of obesity

Table 1.3. Current status of various antiobesity investigational new drugs [19]

Drug	Mechanism	Stage of development	Sponsor
NNC0165-1562	Peptide YY analogue	Phase I	Novo Nordisk
Semaglutide	GLP-1 receptor agonist	Phase III	Novo Nordisk
MED10382	GLP-1 and glucagon receptor agonists	Phase II	MedImmune
SAR425899	GLP-1 and glucagon receptor agonists	Phase I	Sanofi
NNC0090-2746	GLP-1 and GIP receptor agonists	Phase I	Novo Nordisk
LY3298276	GLP-1 and GIP receptor agonists	Phase II	Eli Lilly
LY2405319	FGF21 protein	Phase I	Eli Lilly
Pegbelfermin	FGF21 protein	Phase II	Briston-Myers Squibb
PF-05231023	FGF21 protein	Phase I	Pfizer
GT-001	PYY	Phase I	Gila Therapeutics
AZD7687	DGAT-1 inhibitor	Phase I	Astrazeneca
Licogliflozin	SGLT 1/2 inhibitor	Phase II	Novartis
Leucine-Metformin-Sildenafil	Sirt1 activators	Phase II	NuSirt
Tesofensine	Noradrenaline, dopamine, serotonin uptake inhibitor	Phase III	Saniona
ZGN −1061	MetAP2	Phase II	Zafgen

PYY: Peptide YY; GLP-1: glucagon-like peptide 1; GIP: Glucose-dependent insulin tropic peptide: FGF21: Fibroblast growth factor 21; DGAT1: Diacylglycerol acyltransferase 1; SGLT 1/2: Sodium glucose co-transporter 1/2; Sirt1: Sirtuin 1; MetAP2: Methionine Aminopeptidase 2

Thus, the currently available clinical drugs and drug candidates under clinical trials predominantly focus on central pathways. Orlistat acts on peripheral target, where it inhibits Pancreatic Lipase (PL). In the current scenario, the major reason for obesity is the difference between energy intake and energy expenditure. Dietary fats play a prominent role in the energy supplement. Hence, the reduction in the breakdown of triglycerides into monoglycerides *via* inhibition of PL is a promising strategy for the treatment and

management of obesity. Further, PL inhibitors do not need any systemic absorption, that offers an additional advantage of diminishing the possibility of adverse effects.

1.2. Fat-rich diet and role of PL in obesity

The development of obesity is closely associated with the intake and metabolism of fat/triglyceride contents. Exogenous fats cannot be directly used by the body; hence various biochemical reactions [20–22] are essential for the absorption of dietary triglycerides in the gastrointestinal tract (**Fig. 1.4**).

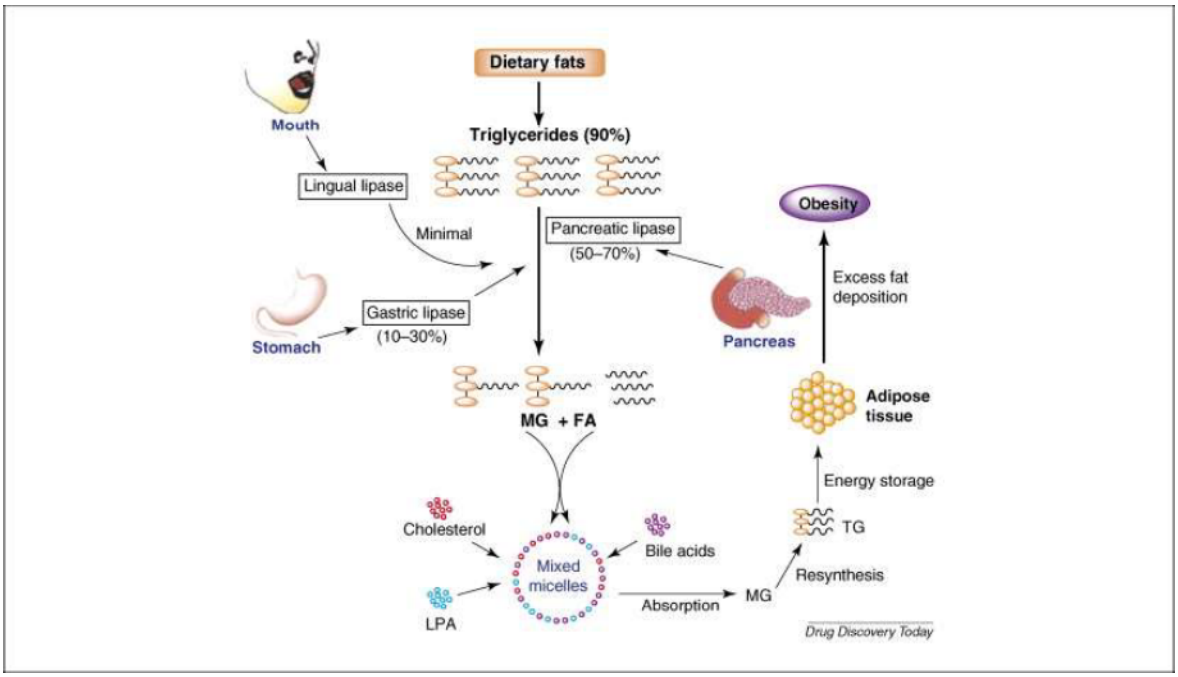


Fig. 1.4. The physiological role of PL in lipid digestion. Adapted from [20] with permission
MG- monoglycerides; FA- Fatty acids; TG- Triglycerides; LPA- Lysophosphatidic acid

Human lipase superfamily includes the pre-duodenal (lingual and gastric) and extra-duodenal (pancreatic, hepatic, lipoprotein and endothelial) lipases. After the triglyceride-rich diet is ingested, the lipids are hydrolysed by these lipases into monoglycerides and free fatty acids. Lingual lipases (secreted from the serous gland) play a small role in the degradation of fats in adults, while in infants and young children it is responsible for 50-70% of fat digestion. Gastric lipase accounts for 10-30% fat digestion. It is secreted in response to the mechanical stimulation and ingestion of fat containing food etc. Gastric lipase is primarily involved in the hydrolysis of short-chain esters. The incomplete breakdown of dietary fats in the stomach forms larger fat globules that undergo hydrolysis by PL. However, the fatty acids generated during the gastric lipolysis act as emulsifiers

alongside the bile salts, for the digestion of long-chain fatty esters in the duodenum. PL adheres non-specifically to the surface of these insoluble substrates and results in their breakdown into monoglycerides and free fatty acids. Lipid mixed particles, such as bile acids, cholesterol etc are absorbed by the small intestine. Further re-synthesis of triacylglycerol occurs which is then stored in the adipose tissue.

PL is the key enzyme responsible for the digestion of 50 - 70% of dietary triglycerides. PL is secreted by pancreatic acinar cells into the duodenum. For the normal digestion process, PL requires a cofactor enzyme, colipase, that is produced from the cleavage of Procolipase (secreted by the exocrine pancreas) by procolipase propeptide (APGPR). Colipase binds to the C-terminal of PL without any conformational changes. The optimal activity of PL is reported at pH of 8.5 but it is found to be very active in pH 6.5 and least active in lower pH.

1.2.1. Crystal structure of PL

PL (also known as the pancreatic triacylglycerol lipase) is classified under the family of serine hydrolases (EC 3.1.1.3). The human PL is encoded by the *PNLIP* gene located at 10q25.3 region of the chromosome and is secreted from the pancreatic exocrine, along with the other pancreatic enzymes [23,24]. The crystal structure of HPL (human pancreatic lipase) reveals that the inactive form of HPL is a single chain glycoprotein containing 449 amino acids folded into two domains. The larger *N*-terminal typically appears as α/β structure comprising 1–335 residues that holds the active catalytic site. The smaller C-terminal is sandwiched by the two layers of β sheet. Normally, the active catalytic site comprises of a catalytic triad of the amino acids, Ser152-Asp176-His263. The PL tends to lose its activity upon chemical modification of Ser152 which is located in the edge of the N-terminal and C-terminal. This catalytic triad is highly restricted and is surrounded by the hydrophobic lid domain which consists of the amino acids Gly76-Lys80 and Leu213-Met217, that protects the access of solvents and substrates to the active sites. However, the activation of the PL leads to a conformational change in the lid domain, resulting in the opening of the active site (**Fig. 1.5**). The conformational change is further facilitated through a salt bridge formation by Arg256-Asp257 with Tyr267-Lys268 [25]. Crystal structures of both the conformation have been identified by X-ray diffraction, and deposited in the PDB with an ID of 1LPB (open conformation) [26] and 1N8S (closed conformation) [27].

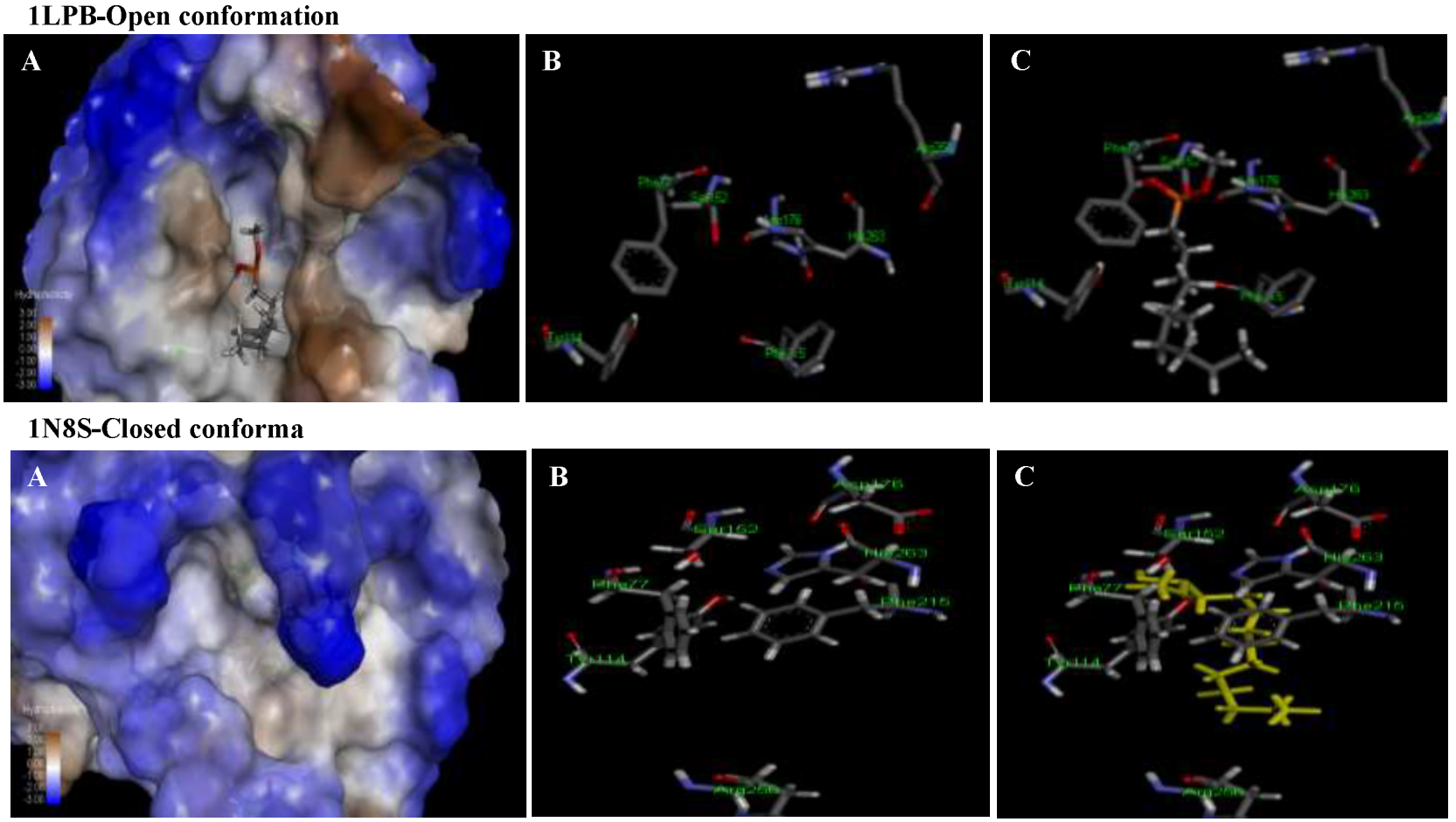


Fig. 1.5. Representation of open and closed lid forms of human PL

A - hydrophobic surface representing the closed and open lid conformations (in brown); B – Amino acid alignment in the active site; C-ligand present in the active site, yellow represents the ligand in active site represent the steric hindrance by closed conformation.

1.2.2. Clinically approved PL inhibitor

1.2.2.1. Orlistat

Orlistat is the only PL inhibitory drug available in the management of obesity. It is a tetrahydro derivative (saturated derivative) of lipstatin obtained from the bacterium *Streptomyces toxytricinii*. United States Food and Drug Administration (USFDA) approved the use of orlistat as an anti-obesity drug in 1997 and till 2012, orlistat was the only anti-obesity medication approved for long term treatment of obesity [3,28].

Structurally orlistat contains a lactone ring, that is attached to two hydrocarbon chains. Orlistat exerts an inhibitory effect by covalently binding to a serine residue at the active site of the lipase (**Fig. 1.6**). During the interaction with PL, the lactone ring gets opened and forms a hydroxy ester linkage with the nucleophilic Ser 152 [29].

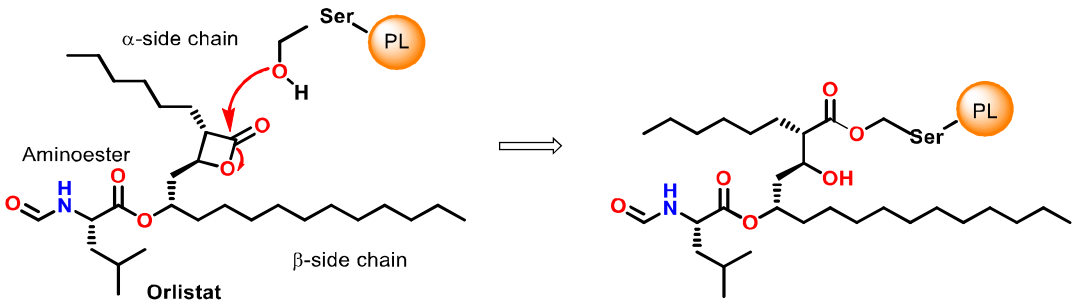


Fig. 1.6. Mode of action of Orlistat

On an average, 120 mg of orlistat when taken *t.i.d*, decreases fat absorption by ≈10%. The recommended dose of orlistat is 120 or 60 mg capsule *t.i.d* with each meal containing fat. The latest research shows that orlistat reduces the absorption of certain fat-soluble vitamins such as A, D, and E and certain fatty acids, such as arachidonic acid (ARA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) in the body [22]. Hence, standard multivitamins and fish oils are prescribed along with orlistat treatment. Chronic administration of orlistat has been reported to elicit mild adverse effects including flatulence, faecal urgency, oily spotting, oily defecation, fatty/oily stool, increased defecation and faecal incontinence etc. However, the recent decade has seen considerable reports on the severe adverse effects produced by chronic administration of orlistat, that includes hepatotoxicity and nephrotoxicity. In response to these severe adverse effects, FDA Center for Drug Evaluation and Research, in 2015, approved safety labeling changes

for orlistat, that included mentioning of various adverse effects and possible risks *viz.*, kidney stones, gall stones, liver injury and pancreatitis [30 32]. The safety and effectiveness of orlistat for long-term weight maintenance, cost-effective treatment, overall fat-related morbidity and mortality has yet to be understood.

1.2.2.2. Cetilistat

Cetilistat is a highly lipophilic benzoxazinone derivative (**Fig. 1.7**) that inhibits PL. Reports suggests that it is well tolerated than orlistat [33].

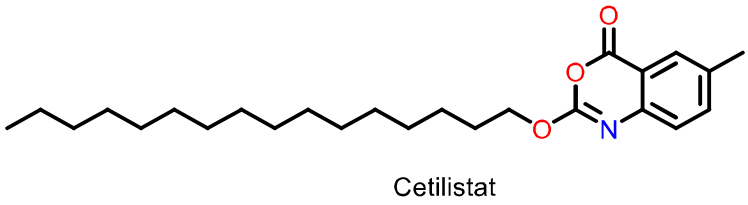


Fig. 1.7. Structure of Cetilistat

Cetilistat has successfully completed its phase III clinical trial and has been approved for the treatment of obesity with complications, by the Japanese Ministry of Health, Family and Welfare on September 20, 2013 [34,35]. However, as on date there are no reports available on its USFDA approval.

1.3. Problem Statement

Obesity is growing at an alarming rate causing high percentage of mortality. Unfortunately, there are only few treatments/interventions available that are effective and safe in management of obesity. Amongst the various putative targets used in the management of obesity, inhibiting fat accumulation *via* PL inhibition is a fascinating approach towards developing newer and safer anti-obesity drugs. Since, PL exerts its activity only in the intestine, its inhibition does not directly involve any systemic effect. This offers an additional advantage of diminishing side/adverse effects and complications. Hence, PL inhibition offers a comparatively safer drug strategy in the management of obesity. The above-discussed facts clearly indicate the limitations of obesity treatment in the form of few approved drugs, limited drug efficacy and significant adverse effects of the available drugs. These events highlight the necessity for the development of new, safer and effective anti-obesity drugs acting *via* PL inhibition.

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