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Chapter

The Multiple Causes of Obesity

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Abstract

Obesity is known to cause physical and metabolic diseases. It is often assumed by people (including the healthcare workers) that the person with obesity lacks self-control in matters of diet and physical exercise, and is therefore responsible for his or her weight. Persons with obesity have to face sarcasm, barbs, and discrimination due to their condition. They often have difficulty in getting jobs or have to accept lower than standard pay for their work. Although weight gain requires calorie intake in excess of calorie expenditure, it is sometimes not easy for the person to restrict calories due to the underlying causes of obesity. The body resists losing weight, and attempts to hoard calories by reducing the metabolic rate. In this chapter we have explained and classified the causes of obesity into endogenous and exogenous. The endogenous causes include genetic and epigenetic causes, maternal factors, and hormonal causes, while exogenous causes include obesogenic environment, life-style, and weight-gain promoting medicines. It must be realized that losing weight and keeping it off is not easy for a person with obesity.

Keywords: Obesity, Endocrine causes of obesity, Endogenous causes of obesity, Exogenous causes of obesity, Genetics of obesity

1. Introduction

Calorie intake that exceeds body requirements results in storage of the excess calories in the body. Although proteins are highly versatile in function, they cannot be used to store excess energy. The amount of glycogen that can be stored in adult liver is 100–120 grams, the skeletal muscle can store about 400 gram glycogen in a 70 kg adult. Small amounts are also present in other cells. The triacylglycerols (TAGs) are the best suited for energy storage purpose: they are energy-dense, hydrophobic (therefore do not associate with space-filling calorie empty water molecules), and can be stored in huge amounts. However, excess storage of the TAGs is often associated with ailments and early mortality. The Obesity Medicine Association has defined obesity as a 'chronic, relapsing, multi-factorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences' [1]. Since measurement of body fat content is tedious and requires sophisticated instruments, it is easier to define overweight and obesity on the basis of the Body Mass Index (BMI). BMI is calculated easily by dividing the weight of the person in kilograms by the square of height in meters. According to the World Health Organization, persons with BMI < 18.5 kg/m^2 are underweight, those with BMI 18.5 to < 25 kg/m^2 fare of

normal weight, those with BMI 25 to < 30 kg/m^2 are overweight, and those with BMI > 30 kg/m^2 are obese [2]. Besides affecting the patient on the individual level (posing increased risk of obesity-related diseases), obesity affects families and nations in terms of healthcare requirements, reduced working capacity, and economic burden. Annual healthcare costs for obesity exceed $700 billion [3]. With the global increase in the incidence of obesity and obesity-related diseases, healthcare costs for obesity have exceeded those for smoking [4].

Thermodynamics can explain the excess storage of TAGs in a simple, succinct manner: storage of calories occurs when calorie intake exceeds calorie expenditure. Decreasing the intake and increasing the expenditure should melt away the excess fat. Research conducted in the past 70 years reveals that adipose tissue that has grown out of size wants more of itself and persuades the body to devise ways to hoard calories. Thus, obesity is not merely a case of poor self-control. Also, all persons with obesity do not develop obesity-related diseases, as the type of adipose tissue and the site of deposition influence the risks to health.

2. Identifying obesity and determining the adipose content

The fact that weight is related to longevity of the person was realized by life insurance companies [5]. A higher health risk was predicted for weight more than 20% the ideal weight for that height. This is equivalent to a BMI of 27.8 kg/m^2. BMI cannot differentiate muscle from fat, or inform about the distribution of fat. It cannot detect changes in body composition due to sarcopenia or osteopenia. It has been observed that some races are at a higher risk of type 2 diabetes mellitus and cardiovascular diseases at BMI values lower than what are normal for persons of European descent. Distribution of body fat is different in different races, Asians tend to have more central adiposity compared to the Caucasians [6]. Males have higher lean mass and bone mineral mass compared to females, however, females have more peripheral distribution of fat [7]. Pregnancy, age, and menopause cause redistribution of body fat, promoting central obesity [8]. It is important to determine the fat content of the body as well as the distribution of the body fat. The best method for determining fat content and fat distribution is cadaver analysis, as no in vivo technique can be that accurate [9].

Anthropometric methods are the most convenient and most popular for estimating the extent of fatness. Besides BMI, these include waist and hip circumferences, waist-to-hip ratio (WHR), skin fold thickness, and waist-to stature ratio (WSR). Since shorter individuals usually weigh less, weight alone cannot be used as a criterion to determine the amount of fat stores. WSR and waist circumference are easy and relatively accurate techniques to estimate visceral fat [10]. The body adiposity index (BAI) does not require weight measurement; it is the ratio of hip circumference to height. It is a fairly accurate measure of adiposity and can be easily used in remote areas without accessibility to reliable scales [11].

According to the two compartment (2C) model, the mass of the human body can be categorized into anhydrous Fat Mass (FM) and Fat Free Mass (FFM). The FFM includes water, minerals, and proteins. FM is assumed to have a density of 0.9007 g/cm^3 while the FFM is assumed to have a density of 1.1000 g/cm^3. Water content of the body is assumed to be 73.72% [12]. Techniques based on two-component model are bioelectric impedance analysis, whole body counting of total body potassium, densitometry methods (hydrostatic underwater weighing and air displacement plethysmography), and hydrometry using isotope dilution technique. The water content (hydration fraction), bone mineral content, and density of the FFM vary with age, pubertal status, and pregnancy. These values are altered in patients with

deranged hydration and in those who have recently lost weight. Differences related to ethnicities have also been observed.

In the 3 compartment (3C) model of body composition assessment, the FFM is sub-divided into lean tissue mass (LTM) and bone mineral content (BMC). This method requires densitometry as well as hydrometry measurements and includes dual energy X-ray absorptiometry (DEXA), a rapid non-invasive method for regional as well as whole body measurement in which high- and low-energy X-rays are transmitted through the body.

The 4 compartment model further categorizes LTM into total body water (TBW) and protein. It requires a combination of several measurement techniques: hydrodensitometry like under-water weighing or air-displacement plethysmography (to measure fat), DEXA (to measure mineral), isotope dilution (to measure water), and residual techniques (to measure protein) [13, 14]. It is an expensive, elaborate, and time requiring technique.

Multi-component models have also been used that incorporate results from many techniques, and are therefore more accurate. Simple methods can be used in the field, while lab-based methods or CT, MRI, X-ray techniques can be used only in clinical settings.

Anthropometric methods and bioelectric impedance analysis are considered indirect methods of assessment. Direct methods include measurement of total body water by isotope dilution technique, total body counting to measure radioactive potassium, and neutron activation techniques with a body scan to measure different elements. Criterion methods include underwater weighing, air-displacement plethysmography, DEXA, computed tomography (CT) scan, and magnetic resonance imaging (MRI) [15].

Vague in 1947 [16] noted that pear-shaped body with higher fat distribution in hips and thigh regions is associated with protection against metabolic diseases. Deposition of fat in the abdominal region (usually seen in males) is associated with development of metabolic diseases [17, 18]. Most of the adipose tissue in the adult human is white adipose tissue (WAT), the main function of which is to store excess calories as triacylglycerols. The brown adipose tissue (BAT), present in small quantities in the interscapular region, is responsible for non-shivering thermogenesis. WAT present in visceral regions is called visceral adipose tissue (VAT), and that present below the skin for insulation is called subcutaneous adipose tissue (SAT). Excess VAT is associated with the metabolic complications of obesity, like metabolic syndrome, type 2 diabetes mellitus, dyslipidemia, and cardiovascular diseases. TAGs may deposit in tissues other than the adipose; this is called ectopic fat. Ectopic fat in viscera, heart, and vasculature can be seen in lipodystrophy, characterized by little subcutaneous fat and high amounts of ectopic fat. Deposition of thoracic periaortic fat and peripheral artery disease is considered local toxic effect of the ectopic fat. The renal sinus fat has been associated with hypertension and chronic kidney disease [19]. Although BMI is the most common method to identify overweight and obesity, it is unable to differentiate VAT and SAT, and central and global obesity. CT and MRI can be used to quantify the amount of visceral fat accurately. DEXA can also be used, however, it tends to underestimate VAT in people with normal BMI, and overestimates VAT in people with severe obesity [20].

It has been noted that some individuals classified as overweight or obese according to their BMI do not show insulin resistance or increased risk of metabolic diseases. Such people are said to have metabolically healthy obesity (MHO), which can be a transient stage of variable duration that progresses towards metabolically unhealthy obesity (MUO) [21]. A person with obesity can be classified as metabolically healthy if blood pressure, blood glucose, TAG, and high density lipoprotein cholesterol levels are normal without medication [22]. Metabolically unhealthy

obesity results when adipocytes of SAT are unable to proliferate and differentiate. Such tissue shows hypertrophy instead of hyperplasia, leading to ectopic and visceral deposition of fat.

3. What causes overweight and obesity?

The imbalance between energy intake and expenditure can result from various causes that can be broadly classified into endogenous and exogeneous. In his paper on obesity, Pennington has described how the concept of endogenous obesity originated in 1907 [23].

3.1 Endogenous causes of obesity

Genetic and epigenetic disorders, hormonal imbalances, maternal and birth-related factors, microbiome, and infections are included in the endogenous causes of obesity. In case of children, pathologic cause can be suspected if the patient shows hyperphagia with absence of satiety signals, shows food-seeking behavior, hides or steals food, has neuroendocrine abnormalities, has skin and hair that are lighter than those of siblings, or is gaining weight rapidly before the age of 5 years.

3.1.1 Genetic causes of obesity

Ethnic differences in obesity have been observed; admixture mapping studies show that obesity correlates with percentage of ancestry derived from ethnic groups [24]. Studies on individual families and animal models revealed rare obesity causing genes like leptin and leptin receptor genes, melanocortin 4 receptor gene, and the proopiomelanocortin genes, etc. Studies on obesity concordant monozygotic twins show BMI and other anthropometric measures like WHR are 40–60% heritable in children and adults [25]. The genome-wide association studies (GWAS) using massive study populations identified 119 independent loci associated with BMI [26]. The human obesity gene map discussed by Rankinen et al. [27] lists single-gene mutations in 11 different genes, 50 loci related to Mendelian syndromic obesity, 253 quantitative trace loci (QTL) for obesity-related phenotypes. On the basis of clinical presentations, genetic obesity can be classified into monogenic non-syndromic, monogenic syndromic, and polygenic obesity.

A. **Non-syndromic monogenic obesity.** Rare, early-onset severe obesity that is mainly caused by mutations in genes whose products are involved in the regulation of food intake. Most mutations require two dysfunctional copies of genes as homozygous or compound heterozygous condition in order to affect the phenotype. Around 200 single gene mutations have been associated with human obesity, but all are confined to more than 10 genes.

1. **Leptin.** The name leptin has been derived from the Greek word 'leptos' which means 'thin'. Leptin (product of *ob* or *LEP* gene) is a 167 amino acid protein synthesized mainly in the adipocytes and enterocytes, and also in gastric epithelium and placenta. It is also called the satiety hormone as it regulates fat stores by diminishing hunger. Since its discovery in 1994 [28], leptin has been considered a potential target in the treatment of obesity.

   Mutations in leptin gene are very rare, lead to hyperphagia and obesity, and can be ameliorated by leptin administration [29]. Administration of exogenous leptin reduces hyperphagia that is spontaneous or induced by

fasting [30]; chronic administration causes weight loss by reducing food intake [31, 32]. In most persons with obesity, circulating leptin levels are high, indicating that leptin resistance rather than leptin deficiency is the underlying reason for weight gain.

2. **Leptin receptor.** Multiple isoforms of leptin receptor (Ob-R or LEPR) have been identified, which are produced by alternative splicing of the mRNA or by post-translational modifications [33]. Ob-Rb, the long form of leptin receptor expressed widely in the hypothalamus and appetite-modulating pathways of brain stem, has an intracellular domain that binds Janus kinases (JAK) and signal transducers and activators of transcription (STAT)-3 factors [34, 35]. The activated JAK–STAT-3 pathway induces expression of suppressor of cytokine signaling (SOCS)-3. SOCS are a family of eight proteins that negatively regulate the JAK–STAT pathway, i.e., the very pathway that increases their synthesis.

   Obesity-related leptin-resistance may be due to overexpression of the SOCS-3. This has been supported by the fact that *SOCS-3* deletion in specific neurons in mice [36] or mice with heterozygous global *SOCS-3* deficiency [37, 38] are more leptin-sensitive and resistant to weight gain. Ob-Rb, the long form of leptin receptor, is expressed in the arcuate nucleus of the hypothalamus in two neuronal groups: orexigenic neurons expressing neuropeptide (NP)Y and agouti-related peptide (AgRP), and by anorexigenic neurons expressing proopiomelanocortin (POMC) and cocaine-amphetamine-regulated transcript (CART) [39]. Leptin inhibits the expression of the orexigenic peptides NPY and AgRP, and activates the neurons producing the anorexigenic peptides POMC and CART [40, 41], thus reducing food intake. Low circulating levels of leptin lead to increased expression of NPY and AgRP, decreased expression of POMC and CART, and increased hunger. High levels of leptin in blood decrease the expression of NPY and AgRP, increase the expression of POMC and CART, and decrease hunger. Viral-mediated gene expression used to produce chronic leptin overexpression in the arcuate and paraventricular nuclei and ventromedial hypothalamus resulted in reduced food intake [42].

   The secretory isoform of the leptin receptor binds circulating leptin and modulates its biologic availability, while the short isoform of the leptin receptor is involved in the transport of leptin across the blood–brain barrier [43]. Leptin resistance may be due to defect in leptin receptor, or in the transport of leptin across the blood–brain barrier. Such persons have early-onset obesity and hypogonadism, however, the obesity is not as severe as in the case of persons lacking plasma leptin [42]. In rodents, a high-fat diet produces leptin resistance, prior to the weight gain [43].

   Mutations in leptin receptor gene (*LEPR*) produce a phenotype similar to that of leptin deficiency, with normal or high leptin levels [44, 45]. Often, LEPR mutations are accompanied with deficiencies of growth hormone or thyroid hormone [46, 47].

3. **Proopiomelanocortin.** The precursor protein pre-proopiomelanocortin is a 267 amino acid protein synthesized in the corticotrophs and melanotrophs of the anterior and intermediate lobes of the pituitary [48]. A 26 amino acid signal peptide is removed to form proopiomelanocortin (POMC) with 241 amino acids. Cleavage of POMC forms multiple peptide hormones (α-, β-, and

γ-melanocyte stimulating hormones (MSH), adrenocorticotropic hormone (ACTH), and β-endorphin). The cleavage is brought about by pro-hormone convertase (PC)1/3 (encoded by PCSK 1 gene in humans), carboxypeptidase (CP) E, and other enzymes. Mutations in PCSK1 and CPE are known to cause monogenic obesities (discussed later). The peptide products are packaged into vesicles and released by exocytosis. The processed products of POMC bind to different types of melanocortin receptors (MCRs), and to the μ-opioid receptor [49]. Five MCRs (MC1R to MC5R) have been identified on the basis of their binding properties and tissue locations. MC1R is mainly located on the melanocytes of skin and preferentially binds α-MSH. ACTH can also bind to MC1R. When ACTH is present at high concentrations, as in Cushing's disease, it can cause hyperpigmentation. MC2R is mainly expressed in the adrenal cortex, and binds only ACTH to activate glucocorticoid synthesis. MC3R binds α-, β-and γ-MSH with equal affinity, is present on POMC neurons in the arcuate nucleus, and acts as an inhibitory auto-receptor. MC4R has a very high expression in the paraventricular nucleus of the hypothalamus and is involved in energy balance (discussed later). The primary agonist for MC4R is α-MSH released from the anorexigenic POMC neurons in the paraventricular nucleus. The primary antagonist of this receptor is agouti-related protein AgRP), released by the orexigenic AgRP/NPY neurons, also located in the paraventricular nucleus. MC5R is not expressed in the central nervous system. It is expressed in a variety of peripheral tissues during embryogenesis and binds with α-MSH with a slightly higher affinity. The μ-opioid receptor is expressed in the cortex, hippocampus, and brain stem, and in peripheral tissues. It binds β-endorphin mediating analgesic effect, and is also involved in feeding behavior.

Mutations in the *POMC* gene are autosomal recessive and cause early-onset severe obesity accompanied by hyperphagia, adrenal insufficiency, mild hypothyroidism, and red/ginger hair [50]. Very few patients with this condition have been diagnosed worldwide. Heterozygous individuals have intermediate increase in BMI.

4. **Prohormone convertase 1 and carboxypeptidase E.** Prohormone convertase (PC1/3), also called PCSK1 (pro-protein convertase subtilisin/kexin type 1), is present only in neuroendocrine cells and is involved in the conversion of prohormones to active hormones. It is a serine protease, activated by calcium. CPE, also called enkephalin convertase, releases terminal arginine or lysine residues from polypeptides. It is involved in the production of nearly all neuropeptides and peptide hormones.

   Mutations in *PC1/3* gene are extremely rare [51] and cause severe obesity in childhood. Since this enzyme is involved in the maturation of many hormones, its deficiency is also associated with adrenal, gonadotropic, somatotropic, and thyrotropic insufficiency and postprandial insulin deficiency. Proinsulin levels are high. Patients have severe malabsorptive neonatal diarrhea and may show central diabetes insipidus.

   Only a few patients with *CPE* mutations have been identified throughout the world. Such patients have morbid obesity, intellectual disability, type 2 diabetes, and hypogonadotropic hypogonadism [52].

5. **Melanocortin 4 receptor.** This is encoded by the *MC4R*, an intron-less gene with open reading frame of 999 bp located on chromosome 18. The MC4R is

glycosylated and has 332 amino acids. It is mainly expressed by brain cells and by the enteroendocrine cells. Besides the neurons, it is also expressed by the astrocytes in brain [53].

The MC4R plays a key role in weight regulation. It is activated by α-MSH, and cocaine- and amphetamine-regulated transcript (CART) to decrease food intake and increase energy expenditure. The orexigenic peptides neuropeptide Y (NPY) and AgRP are the natural antagonists of MC4R, and increase appetite and reduce energy expenditure by binding to MC4R [54]. Leptin stimulates the secretion of POMC, and inhibits that of AgRP and NPY.

Heterozygous mutations in *MC4R* gene reported in different ethnic groups are associated with dominantly inherited obesity. MC4R deficiency is the commonest monogenic cause of obesity. In a cohort of 500 children with obesity, 5.8% were found to have mutations in the *MC4R* gene [55]. Homozygous mutations and double heterozygous mutations are rare; about 25% mutations are heterozygous frame shift or nonsense with complete loss of function. Around 20% of the missense mutations are non-pathogenic. Heterozygous carriers of *MC4R* mutations have hyperphagia, impaired satiety, hyperinsulinemia, higher bone mineral density, and higher stature (big boned), especially in childhood. Patients homozygous for the condition have severe obesity and hyperinsulinemia which can be blocked by the administration of an α-adrenergic blocker. The hyperinsulinemia shows an age-related decrease and parallels amelioration of hyperphagia. Adults with MC4R deficiency have lower blood pressure and heart rate than age and BMI matched controls suggesting impaired activation of sympathetic nervous system. Diet-induced weight loss is not easy, but can be achieved by bariatric surgery in heterozygous persons. Liraglutide promotes weight loss in patients with MC4R deficiency.

6. **Single-Minded Homolog 1 (SIM1).** The single-minded (sim) is a basic helix–loop–helix-PAS domain transcription factor in *Drosophila melanogaster* that regulates gene expression in midline cells in the embryo [56]. SIM1, the human homolog, may have pleiotropic effects during embryogenesis. The *SIM1* gene is located on chromosome 6; chromosomal abnormalities like deletion of 6q16.2 region, translocation between 6q16.2 and 1p22.1, or point mutations in the 6q16.2 region cause severe childhood obesity or SIM1-related Prader-Willi-like syndrome. Homozygous SIM1 knockout mice do not survive due to absence of hypothalamic neurons [57].

7. **Brain Derived Neurotrophic Factor (BDNF).** BDNF, also called neurotrophin and abrineurin, is encoded by the *BDNF* gene on human chromosome 11 [58]. The BDNF preproprotein with 247 amino acid residues is processed to mature 119 amino acid protein. Pro-BDNF can be stored in dendrites and axons and undergoes cleavage either inside or outside the cell. BDNF and pro-BDNF are associated with opposing functions. High levels of BDNF are present in the hippocampus, amygdala, cerebellum, and cerebral cortex. Lower levels have been detected in the liver, heart, lung, etc. BDNF is a member of the neurotrophin family of growth factors required for the differentiation, maturation, and survival of neurons. In adverse conditions like hypoglycemia, cerebral ischemia, neurotoxicity, and glutamatergic stimulation, BDNF has a neuroprotective effect. It is also involved in plastic changes related to learning and memory [59].

Receptors for BDNF include TrkB, encoded by the *NTRK2* gene, and LNGFR (low affinity nerve growth factor receptor). The TrkB receptor belongs to the family of tyrosine kinase receptors and is coupled to the Ras, Cdc42/Rac/RhoG, MAPK, PI3K, and PLC-γ signaling pathways. Binding of BDNF with TrkB causes autophosphorylation of TrkB and is important for the development of short term memory and growth of neurons. LNGFR is also called p75. Pro-BDNF preferentially binds to LNGFR, leading to NFκB receptor activation, triggering apoptosis pathway.

WAGR syndrome involves disorders of many body systems and is named for its main features: Wilms tumor (a childhood kidney cancer), aniridia, genitourinary anomalies, and intellectual disability (formerly referred to as mental retardation). A subtype of the WAGR syndrome called WAGRO (characterized by childhood onset obesity) has been reported to be strongly associated with haploinsufficiency for BDNF [60]. Nineteen patients with deletions in any portion of the *BDNF* gene were reported to become obese by 10 years of age.

8. **NTRK2.** The *NTRK2* gene encodes TrkB receptor for BDNF. In case of mice, homologous *NTRK2* mutations are lethal. Heterozygous missense mutations in *NTRK2* have been reported in patients with severe hyperphagia, obesity, impaired nociception, and intellectual disability [61].

9. **Kinase Suppressor of Ras 2.** This protein is a molecular scaffold that coordinates Raf/MEK/ERK signaling and regulates activation of AMP-kinase. It is a product of *KSR2* or the *Fat* gene located on chromosome 12q. Both KSR 1 and KSR2 phosphorylate Raf, MEK, and ERF at several serine and threonine residues and cause their activation [62]. On stimulation by growth factor, the KSR proteins translocate to the plasma membrane to regulate the dynamics of Ras–Raf–MEK signaling.

   Targeted deletion of *Ksr2* in mice leads to obesity with hyperinsulinemia and low glucose tolerance.

10. **SH2B Adaptor Protein 1.** The Src homology 2b family members are adaptor proteins for several members of the tyrosine kinase receptor family. They contain SH2 and PH domains and can form homo or hetero dimers via their N-terminal dimerization domains. The SH2 domain present on the C-terminus binds proteins phosphorylated at their tyrosine residues: TrkA, insulin receptors, IGF2-receptors, insulin receptor substrate (IRS)-1 and 2, and JAK2 [63].

    The SH2B1 is a product of the *SH2B1* gene located on chromosome 16p. It stimulates JAK2 activity and assembles JAK2/IRS1/2 complex to enhance leptin signaling. It also enhances catalytic activity of insulin receptor and protects IRS from dephosphorylation, thus increasing insulin signaling. Deletion of SH2B1 in mice leads to leptin resistance, hyperphagia, obesity, insulin resistance, and type 2 diabetes.

    Several *SH2B1* mutations have been associated with obesity in humans and are known to increase the risk of type 2 diabetes mellitus. Partial deletions of about 200 bp are associated with early-onset severe obesity, while larger interspersed deletion extending through a 593 kb region on chromosome 16p11.2-p12.2 has been associated with developmental delay, feeding difficulties, dysmorphic facial features, and obesity [64].

11. **Adiponectin.** This 244 amino acid protein is also called adipocyte complement-related protein (Acrp), GBP-28, apM1, and adipo Q [65]. The *ADIPOQ* gene is present on chromosome 3. This hormone is produced mainly by the adipocytes and also by other tissues like osteoblasts, liver, myocytes, epithelial cells, and placenta. It is secreted as trimer, (67 kDa, also called low molecular weight or LMW), hexamer, and a multimer with at least 18 monomers (300 kDa, high molecular weight or HMW). Globular adiponectin is generated from full length adiponectin by proteolysis. Plasma levels of adiponectin are inversely proportional to the amount of adipose. Adiponectin levels are high after weight loss due to calorie restriction or gastric bypass surgery in patients with obesity [66, 67], and also in patients anorexia nervosa [68].

    Administration of adiponectin to rodents, and transgenic mice with increased adiponectin showed increased energy expenditure and oxygen consumption without affecting food intake [69, 70]. Adiponectin has been shown to suppress obesity [71], insulin resistance, type 2 diabetes [72, 73], atherosclerosis, and non-alcoholic fatty liver disease [74].

    Adiponectin receptor AdipoR1 is more in the skeletal muscle, and AdipoR2 is more in the liver. Expression of receptors is proportional to insulin levels, and in case of receptors on the muscle cells, the number is increased with exercise [75]. AdipoR1 has a higher affinity for globular adiponectin while AdipoR2 has higher affinity for full length adiponectin. The T-cadherin receptor for adiponectin recognizes hexameric and HMW forms of adiponectin. It is present in the vasculature and is involved in the cardioprotective action of adiponectin. Action of adiponectin on receptor requires adaptor proteins APPL1 or its isoform APPL2.

    Binding of adiponectin to its receptor leads to activation of the AMP-activated protein kinase (AMPK) and the mitogen-activated protein kinase (MAPK). This causes increased NO production, adiponectin-induced glucose uptake, degradation of ceramide by ceramidase, and fatty acid oxidation, ultimately increasing insulin sensitivity.

    Adiponectin deficiency has been associated with increased atherosclerosis while increased expression of adiponectin protects against atherosclerosis in mice [76]. Thiazolidinediones (TZD) used in the treatment of type 2 diabetes mellitus, are known to activate transcription factor peroxisome proliferator-activated receptor (PPAR)-γ, which has been shown to increase adiponectin levels in plasma [77].

    Adiponectin mutations have been associated with type 2 diabetes mellitus [78] and hypoadiponectinemia [79]. Recently, mutation in ADIPOQ has been associated with early-onset obesity and metabolic syndrome [80].

12. **Adenylate Cyclase Type 3.** Adenylate cyclase type 3 belongs to the adenylate cyclase family of enzymes that synthesize cAMP from ATP. The gene for this enzyme *ADCY3* is located on chromosome 2 and codes for a 1144 amino acid protein. The protein shows highest expression in lungs and placenta, intermediate expression in brain, heart, kidney, and skeletal muscle. Lowest expression is seen in liver and pancreas. It is also present in the olfactory cilia. Saeed et al. [81] reported loss-of-function mutations in *ADCY3* gene in 4 severely obese children from 3 consanguineous Pakistani families, and in

an obese boy from a non-consanguineous European American family. Interestingly, a gain-of-function mutation in *ADCY3* gene in a line of N-ethyl-N-nitrosourea (ENU)-mutagenized mice, Jll, with dominantly inherited resistance to diet-induced obesity, protects mice from diet-induced obesity [82].

13. **Other Monogenic Causes of Obesity.** Mutations in the *INSIG2* gene [83, 84] and in gene for peroxisome proliferator-activated receptor gamma (PPAR-γ) [85, 86] are associated with obesity. INSIG2 gene present on chromosome 2 encodes for insulin-induced gene 2 protein which is involved in lipid homeostasis. The gene for PPAR-γ (*PPARG*), present on chromosome 3p, can be activated by fatty acids and their metabolites. The protein is produced predominantly in liver and adipose and is crucial for the differentiation of fat cells. Besides obesity, mutations in this gene can cause insulin resistance, hypertension, and certain cancers.

    Insulin-sensitizing drugs thiazolidinediones are potent agonists of PPAR-γ. This can also lead to increased adiponectin levels (see above).

B. Syndromic Obesity. Patients with obesity (children or adults) who also show cognitive delay, dysmorphic features, organ-specific abnormalities, hyperphagia, and/or signs of hypothalamic dysfunction are considered to have syndromic obesity. Syndromic obesity may show autosomal or X-linked inheritance pattern, or may occur due to de novo mutations. Since comorbidities are present that require additional treatment, it is important to correctly diagnose syndromic obesity, which can be of the following types:

1. **Fat Mass and Obesity-Associated Protein (FTO) or Alpha-Ketoglutarate-Dependent Dioxygenase Deficiency.** This enzyme is coded by the *FTO* gene located on chromosome 16 in humans. The FTO proteins participate in adipogenesis and tumorigenesis and FTO inhibitors have been found to have anti-obesity and anti-cancer effects in vivo. *FTO* is one of the genes known to contribute to polygenic obesity. In fact, it was the first one to be identified by genome wide association studies (GWAS) [87]. In humans, complete deficiency of FTO is associated with an autosomal recessive syndrome with growth retardation, malformations, and premature death. A loss-of-function non-synonymous mutation at position 316 in the *FTO* gene in which arginine is replaced by glutamine has been identified in nine members of a Palestinian family. The afflicted members showed post-natal growth retardation, dysmorphism of head and face, psychomotor delay, and in some patients, brain, cardiac, genital, and palate defects. Complete/partial inactivation of *FTO* gene in mice protects from obesity while overexpression leads to increased food intake and obesity. Evidence suggests that certain mutations of *FTO* may increase the risk of obesity in humans.

2. **Prader-Willi syndrome (PWS).** This is caused by loss-of-function mutation of specific genes on chromosome 15 [88]. In most cases, a part of chromosome 15 from the father is deleted. In some cases, the patient lacks father's chromosome 15 and has two copies from the mother. Some parts of the mother's chromosomes are turned off by imprinting. This is usually not an inherited condition and affects 1 in 10,000 to 1 in 25,000 neonates. Polyhydramnios, reduced fetal movements, and abnormal fetal position may be present. New born may have hypogonadism, lethargy, poor muscle tone and difficulty in feeding. Afflicted children show delayed milestones, short stature, poor physical coordination,

crossed eyes. Hyperphagia begins between the ages of two and eight years and continues throughout life. The child gains excess weight. Adults with this condition have central obesity, hypogonadism, infertility, subnormal intelligence, extreme flexibility, and light skin and hair. More than 50% patients have strabismus.

3. **Bardet-Biedl syndrome (BBS).** This is a rare pleiotropic, autosomal recessive ciliopathy, the estimated incidence is 1 in 1,60,000 in north European populations [89]. About 16 genes are associated with this disorder, accounting for 80% cases. Diagnosis is based on clinical features: post-axial polydactyly, renal dysfunction, obesity, retinal dystrophy, hypogonadism, and learning difficulties.

   The BBS phenotype is less apparent in the first decade of life and the condition is usually diagnosed in late childhood or early adulthood.

4. **Alstrom syndrome (ALMS).** This is also called Alstrom-Halgren Syndrome [90]. It is a very rare autosomal recessive disorder due to defect in the *ALMS1* gene located on chromosome 2p13. The encoded protein is implicated in ciliary function, control of cell cycle, and intracellular transport. About 900 people with this syndrome have been reported worldwide. This syndrome is characterized by childhood obesity (but normal birth weight), hyperphagia, hyperinsulinemia, and type 2 diabetes mellitus. Other features include progressive cone-rod dystrophy leading to blindness (occurring usually prior to 15 months of age) and sensorineural hearing loss (usually bilateral, beginning in the first decade of life). Otitis media with glue ear has been reported. About 70% patients develop dilated cardiomyopathy during infancy or adolescence. Renal failure, pulmonary, hepatic, and urologic dysfunction are often observed, and systemic fibrosis develops with age. Unlike the Bardet-Biedl syndrome, there is no mental defect, polydactyly, or hypogonadism. Retinal lesion causes nystagmus and early loss of central vision in contrast to loss of peripheral vision first, as in other pigmentary retinopathies. Height is normal or more than normal in children, but growth slows down so that adults are usually of short stature. The symptoms and rate of progression of disease varies in patients, even amongst members of the same family.

5. **Pseudohypoparathyroidism (PHP).** This is a heterogeneous group of very rare endocrine disorders, primarily due to resistance to the parathyroid hormone (PTH) [91]. It was first described by Fuller Albright in 1942 to describe patients with PTH-resistant hypocalcaemia and hypophosphatemia and a constellation of skeletal defects called Albright hereditary osteodystrophy (AHO). Features of AHO (seen in PHP-1a and -1c) include short stature, stocky built, rounded face, short fourth metacarpal and other bones of the hands and feet, and ectopic ossifications.

   Gene encoding the alpha-subunit of the stimulatory G protein (*GNAS1*) is defective resulting in at least 4 different forms of PHP: PHP-1 a, b, and c, and PPHP (pseudo pseudohypoparathyroidism). Molecular defect in PHP-2 is yet to be identified. The exact prevalence of PHP is not known.

6. **Cohen syndrome or Pepper syndrome or Cervenka syndrome.** This was first described by M Michael Cohen Jr. in 1973 in two siblings and one isolated case [92]. More than a hundred cases have been identified over the world, with 35 from Finland [93]

The phenotype in Finnish patients is homogeneous: non-progressive psychomotor retardation, microcephaly, characteristic facial features, myopia, progressive retinochoroidal dystrophy, neutropenia, and cheerful disposition. Non-Finnish patients have a confusing phenotype. Affected persons have low birth weight but develop abnormal truncal fat distribution in teenage. This is an autosomal recessive condition, with mutation in the vacuolar protein sorting 13 homolog B (VPS13B, also called COH1 gene) located on chromosome 8q. This transmembrane protein is involved in vesicle-mediated intracellular protein transport.

7. **Other syndromes associated with obesity.** Down syndrome (trisomy 21) and Turner syndrome (45, X) have been reported to be associated with adult obesity [94, 95].

C. Polygenic obesity. More than an hundred polygenic loci harboring genetic variants associated with overweight and obesity have been identified [96–98]. Polygenic obesity is caused by the cumulative effect of obesogenic environment and weight-gain promoting genes. The contribution of a single gene is very small, of only a few hundred grams, but the combined effect of many such genes in a person can have a significant effect on weight gain. Khera et al. [98] have derived and validated a polygenic predictor of weight gain.

3.1.2 Epigenetic causes of obesity

Although the DNA in every cell of the multicellular organism is the same (exception: mosaicism [99]), the expression of genes is different in different cell types. The mechanisms that regulate the expression of genes can be heritable. Epigenetic modifications are mitotically and meiotically heritable modulation of gene function without changes in the sequence of the DNA [100]. Such modifications allow or silence the expression of specific genes. Epigenetic programming can be influenced by environmental and dietary factors as well as by the gut microbiota.

The epigenetic modifications are brought about by DNA methylation (by DNA methyltransferases, DNMTs, at distinct CpG sites), histone modification (methylation, acetylation, ubiquitination, or phosphorylation), and by short non-coding RNA species called micro-RNAs or miRNAs.

a. **DNA methylation.** The CpG sites where methylation occurs are usually present in the promoter regions of genes. Addition of methyl group hinders the attachment of transcription factors and represses transcription of the gene. Some of these genes are involved in appetite control, obesity, metabolism, insulin signaling, inflammation, and growth. Examples of genes associated with obesity having CpG in the promoter regions are the HIF3A, LEP, ADIPOQ, NPY, IGF-2, IRS-1, and POMC, etc. Increased methylation of LEP gene was found in maternal blood samples with pre-pregnancy obesity and in cord blood samples in neonates small for gestational age and whose mothers continued to smoke during pregnancy [101]. Tobi et al. [102] reported higher LEP methylation in men born after prenatal exposure to wartime (Dutch hunger winter) famine in 1944–1945 compared to their unexposed same-sex siblings.

b. **Histone modification.** Histone modifications control the accessibility of the DNA to transcription factors. The five key regulatory genes of adipogenesis: pre-adipocyte factor-1 (Pref-1), CCAAT-enhancer-binding protein β (C/EBP β), C/EBPα,

PPARγ, and adipocyte protein 2 (aP2), are modulated via histone modification during adipocyte differentiation [103].

c. **Micro RNA.** miRNA are short (18–25 nt) non-coding RNA sequences that regulate gene expression [104]. Certain miRNA species have been identified that are associated with insulin resistance and low-grade inflammation seen in obesity [105]. Childhood obesity is associated with specific miRNAs while some miRNAs are associated with weight changes [106–108].

Epigenetic changes influence embryo formation and development, inactivation of X chromosome in female, genomic imprinting, cell differentiation, stable inheritance of gene expression, and immune cell function. In case of mice it was observed that pregnant animals exposed to polycyclic hydrocarbons during pregnancy gave birth to offspring with higher weight and fat mass. These offspring showed higher expression of PPAR-γ, C/EBP α, Cox2, FAS and adiponectin and lower DNA methylation of PPAR γ. This epigenetic change was heritable, as it was also observed in the subsequent generation [109]. Female mice born following perinatal exposure to bisphenol A showed significantly different DNA methylated regions compared to controls [110].

3.1.3 Maternal factors influencing obesity

Certain factors related to the mother cannot be altered but are known to influence body weight or metabolic processes of the offspring. A U-shaped association between maternal age and fasting glucose concentration in adult offspring has been reported [111]. Adult offspring of younger or older mothers had blood glucose levels higher by about 0.05 mmol/L higher than the reference group. Early maternal menarche [112], maternal diabetes [113], and maternal smoking during pregnancy [114] are associated with a higher BMI in offspring. Low maternal education influences obesity, however, the relationship is different in different ethnicities [115, 116]. Maternal employment has also been found to influence children's weight [117].

3.1.4 Hormonal causes of obesity

Secondary obesity (consequence of some other illness) due to endocrine causes is relatively less common.

1. **Hypothyroidism.** Triiodothyronine (T3) and thyroxine (T4) are tyrosine-derived iodine-containing hormones produced by the thyroid gland that act on almost all cells of the body to regulate a variety of metabolic functions. T4 is converted to the 4-times more potent T3 by deiodinases in cells, however, since T4 has a longer half-life, it is the major form in circulation (ratio of T4/T3 in blood is approximately 14).

   Weight gain has been reported in thyroid insufficiency. About 54% patients with overt hypothyroidism report gain of weight compared to 13.8% control subjects [118]. Hypothyroidism is also associated with dyslipidemia with increased cholesterol levels. The thyroid gland secretes prohormone thyroxine or T4 (3,5,3′,5′-tetraiodothyronine) along with small quantities of active T3 (3,5,3′-triiodothyronine), on receiving the signal from the pituitary gland in the form of thyroid stimulating hormone (TSH) or thyrotropin. TSH is released from the pituitary under the influence of thyrotropin releasing hormone (TRH), the master regulator of thyroid function, produced in the paraven-

tricular nucleus of the hypothalamus. Depending on the underlying cause, hypothyroidism can be primary (decreased production of thyroxine by thyroid due to various reasons), secondary (due to decreased TSH), tertiary (due to deficiency of TRH), and peripheral or consumptive hypothyroidism (due to increased activity of deiodinase 3 which degrades thyroid hormone). Secondary and tertiary hypothyroidism are together called central hypothyroidism [119].

Every organ system and cell in the body is influenced directly or indirectly by the thyroid hormones. Gut motility, heart rate, body temperature, perfusion of lungs, and muscle contraction modulate the effect of catecholamines. In females, thyroid hormones influence menstruation, ovulation, and fertility. Bone growth and brain maturation in children are also influenced by these hormones, while in adults they affect the mood [120]. Thyroid hormones regulate the basal metabolic rate (BMR) and therefore are responsible for increase/decrease/maintenance of body weight.

Decreased thyroxine levels cause accumulation of hyaluronic acid in the dermis which causes water retention and non-pitting edema [121]. Decreased blood flow to kidneys resulting in lowered glomerular filtration rate in hypothyroidism causes water retention and increase in body weight [122]. This is aided by decreased tubular resorption and secretion in thyroxine deficiency. Thyroid hormones also regulate the number of adrenergic receptors and dopaminergic activation of the tubular cells, thus affecting the renin-angiotensin-aldosterone (RAA) axis [123].

Hypothyroidism has been shown to cause decreased mitochondrial biogenesis and decreased levels of uncoupler proteins [124, 125].

Thyroid dysfunction has been associated with decreased insulin sensitivity [126]. This may be a consequence of increased adipose deposition from decreased BMR. Increased adipose tissue is known to cause insulin resistance in obese subjects.

2. **Polycystic Ovarian Syndrome (PCOS).** This is a heterogeneous disorder with ovarian dysfunction, hirsutism, hyperandrogenism, obesity, and insulin resistance. PCOS has multifactorial etiology with both genetic and environmental components [127]. More than 50% of adult women with PCOS are overweight or obese and weight reduction alleviates menstrual irregularity [128]. Weight deposition is more around the waist (android pattern of fat distribution), and is both the cause as well as effect of hyperandrogenaemia [129]. Increased adipose tissue leads to higher production of adipokines. Abnormally high leptin levels have been noted in PCOS [130], although some authors report that the serum levels of leptin correlate with obesity rather than with PCOS [131]. Houjeghani et al. have reported higher levels of insulin, testosterone, luteinizing hormone (LH), and higher LH to FSH (follicle stimulating hormone) ratio in women with PCOS compared to normal age and BMI matched controls [132]. Lower concentrations of sex hormone binding globulins were reported in PCOS.

3. **Cushing Syndrome.** The corticosteroid hormones produced by the adrenal cortex are of two types: glucocorticoids and mineralocorticoids. The glucocorticoids e.g., cortisol affect metabolism of carbohydrates, fats, and proteins, and are involved in anti-inflammation, immunosuppressive, anti-proliferative, and vasoconstrictive processes. The mineralocorticoids like aldosterone are involved in regulation of water and electrolyte balance.

All conditions in which cortisol level is higher than normal are classified under Cushing syndrome, while Cushing disease is pituitary dependent [133]. Cushing syndrome can be classified into ACTH-dependent, ACTH-independent, and pseudo-Cushing syndrome. Cushing disease, ectopic ACTH syndrome, ectopic CRH syndrome, macronodular adrenal hyperplasia, and iatrogenic treatment with ACTH are included in the ACTH-dependent variety of Cushing syndrome. The ACTH-independent Cushing syndrome includes adrenal adenoma and carcinoma, primary pigmented adrenal nodular hyperplasia and Carney's syndrome, McCune-Albright syndrome, aberrant receptor expression, and iatrogenic Cushing caused by pharmacotherapy by steroids. Chronic alcoholism and depression can cause pseudo-Cushing syndrome. A rare condition with repeated episodes of cortisol excess interspersed by regular or irregular periods of normal cortisol secretion is called the cyclic Cushing syndrome.

Chronically elevated levels of cortisol in Cushing's syndrome cause redistribution of fat and central obesity [133]. Glucocorticoids (GCs) increase hypothalamic endocannabinoids, hypothalamic AMPK activity, and gene expression of orexigenic NPY and agouti-related peptide, resulting in increased appetite. GCs promote adipocyte differentiation and sensitize preadipocytes to insulin. Visceral adipose tissue (VAT) shows differential response to GCs: increased deposition and insulin resistance occurs in VAT compared to subcutaneous adipose tissue (SAT). Excess glucocorticoids also produce hyperglycemia, dyslipidemia, and increased protein degradation.

4. **Growth Hormone Deficiency.** Growth hormone (GH) or somatotropin exists as several isoforms; the major isoform is a 191 amino acid protein. Secretion of growth hormone by the somatotropic cells of anterior pituitary is under control of the cells of neurosecretory nuclei of hypothalamus, which release GH releasing hormone (GHRH) or somatocrinin and GH inhibiting hormone (GHIH) or somatostatin. Release of GHRH and GHIH is influenced by physiologic stimulators: sleep, exercise, and nutrition, and by the level of free fatty acids in blood. GH is released in a pulsatile manner, the peak occurs an hour after the onset of sleep. During the day, secretion of GH occurs at 3–5 h intervals [134]. Age, sex, diet, exercise, and stress influence GH secretion, which is also influenced by the other hormones.

   Congenital, acquired, or idiopathic deficiency of GH may be associated with increased adipose deposition, especially in the waist region, and insulin resistance. However, reduced GH levels have been reported in some patients with obesity [135, 136]. Usually, deficiency of GH in children is due to insufficient production of growth hormone releasing hormone in the hypothalamus. Damage to the pituitary or hypothalamus (due to tumor or tumor-related surgery, stroke, bleeding, infection, etc) in adulthood may lead to decreased GH production. GH increases lipolysis in the adipose tissue, and reduces storage of TG in a non-uniform manner. Thus it promotes loss of intra-abdominal fat. Scacchi et al. [137] reported that a primary growth hormone deficiency causes centripetal adiposity, while obesity with increase in visceral adipose tissue produces secondary growth hormone deficiency.

5. **Laron syndrome or primary growth hormone insensitivity (GHI).** GHI [138] is a group of rare disorders caused by mutations either in the GH receptor gene, or in genes of signaling proteins within the cell that are activated on binding of GH to its receptor. Various mutations and their effects have been summarized by Boro et al. [139]. Synthesis of insulin-like growth factor (IGF)-

1 is prevented although GH levels in blood are normal or high. Such children show improved growth when IGF-1 is administered before puberty, but no improvement if only GH treatment is given. Children with GHI show delayed onset of puberty, short limbs, reduced muscle strength and endurance, prominent forehead, low blood sugar, and obesity in adulthood.

6. **Ghrelin (Lenomorelin).** Ghrelin is a 28 amino acid peptide hormone discovered in 1999 by Kojima et al. [140]. It is a fast-acting orexigenic hormone produced by the endocrine cells (ghrelin cells) in gastric fundus and to a lesser extent in the body of the stomach, intestinal mucosa, lungs, urogenital organs, and brain. It has a role in meal initiation. Pre-prandial ghrelin surges occur at fixed feeding schedules, or at food-related cues. The post-prandial decrease in ghrelin levels is due to increased intestinal osmolarity and increased insulin. Ghrelin regulates the input and output of calories, and therefore influences the body weight, via the G-protein-coupled growth hormone secretagogue receptor (GHSR)1a. Besides regulating appetite, ghrelin stimulates secretion of GH and ACTH, increases gut motility and gastric acid secretion, modulates sleep, stress, and anxiety, influences taste sensation and reward-seeking behavior, regulates glucose metabolism, reduces lipid degradation, and suppresses thermogenesis in brown adipose tissue. It has been shown to protect muscle from atrophy and improve cardiovascular function [141].

Two distinct forms of ghrelin are present in blood: acylated ghrelin (AG) and unacylated ghrelin (UAG). About 90% of the circulating ghrelin in unacylated (UAG). The AG acts on GHSR 1a mediating growth hormone release, while UAG acts on GHSR 1a on pancreatic cells stimulating the release of insulin and glucose utilization. AG opposes the action of UAG, inhibiting the release of insulin. In obesity, UAG levels decrease while the AG levels remain unchanged.

Highest levels of ghrelin in blood are immediately before a meal, and drop to lowest levels immediately after the meal. Ghrelin administration increases appetite in both humans and rats. Ghrelin and synthetic ghrelin mimetics bind to the GHSR1a in hypothalamus, brain stem, and in the mesolimbic pathway, cause secretion of orexigenic neuropeptide Y (NPY) and agouti-related protein (AgRP). GHSR 1a is also expressed in vagal efferent neurons. Under influence of ghrelin, the gastric vagal efferents become less sensitive to gastric distension, increasing food intake.

Plasma level of ghrelin is lower in persons with obesity, except in patients with Prader-Willi syndrome, where ghrelin levels are proportional to the food intake. AG and UAG levels were compared in insulin-resistant and insulin-sensitive subjects with obesity. It was found that UAG and total ghrelin was lowered in insulin-resistant subjects, while only AG levels were lowered in the insulin-sensitive subjects [142]. In patients with anorexia nervosa and with cancer-induced cachexia, ghrelin levels are high [143, 144]. Obese rodents with low levels of ghrelin in plasma have reduced levels of ghrelin-receptor mRNA as compared to the normal lean controls. Experiments on rodents showed that central ghrelin signaling activates reward centres in response to alcohol, food, high-fat diet, and psychosomatic drugs like cocaine [145, 146].

Besides being the hunger signal, the ghrelin-GHSR 1a system is related to the rewarding aspects of food intake. It is activated in anticipation of food intake, negative energy balance, and psychological stress. In times of food scarcity, the effect of the ghrelin/GHSR 1a system on the mesolimbic pathway is advantageous for the animal's survival.

In developed countries, as well as in the rapidly developing countries, the changes in environment are favoring sedentary lifestyle, easy availability of calorie-dense tasty affordable foods, and increased stress levels are promoting increased appetite. The action of ghrelin on the mesolimbic system increases the appetite, acting as a spice to further increase food intake. In the current scenario of easy availability of food, the ghrelin/GHSR 1a system is no longer an evolutionary advantage but is in part responsible for the obesity epidemic and the associated diseases [147].

Weight gain may also be influenced by insulin, estrogen, progesterone, prolactin, and melatonin.

3.2 Exogenous causes of obesity

Certain factors that are preventable and influence the person from outside the body are classified as exogenous causes.

3.2.1 Depression, sleep deprivation, gut microbiota, and infections

1. **Depression.** Previously it was believed that depression was associated with a loss of appetite and sleep, with an inability to persuade oneself to cheer up and get going. Later, atypical depression was noted for increased eating, hypersomnia, frequent, relatively short episodes, and a proclivity to obesity [148]. Murphy et al. [149] reported that many patients with depression felt like eating when they felt bad. From their study on 1396 subjects, they concluded that patients with obesity tended to experience more severe depression, compared to the non-obese. It is possible that the stigma of obesity contributed to the depression.

2. **Sleep deprivation.** Lack of sufficient sleep has been reported to be associated with high fat intake, night-time snacking, binge-eating, and gain of weight [150]. Altered sleep patterns due to shift work, trans-continental travel, sleep apnoea, or due to new parenthood can lead to sleep insufficiency. Sleep restriction causes increased fat and carbohydrate intake and increased intake of total calories, with no corresponding increase in energy expenditure. Ding et al. [151] note that sleep dysregulation perturbs appetite-regulating hormones like leptin and ghrelin, affecting eating behavior and metabolism.

3. **Gut microbiota (GM).** Ninety-nine percent of the gut microbiota are bacteria, of which 90% are of the phyla Firmicutes and Bacteroidetes [152]. Some fungal, protozoan, and archaeal species have also been isolated. Some bacteria belong to the phyla Proteobacteria, Actinobacteria, Verrucomicrobia, and Fusobacteria. Most GM share a commensal relationship with the host, enhancing the overall fitness. A 20% increase in Firmicutes and a corresponding decrease in Bacteroidetes is associated with the increase in energy intake, thus inducing obesity. GM composition is involved in diseases like obesity, diabetes, inflammatory and immune disorders, and cancer.

   Type of food taken influences the population of gut biota. High fat Western diet reduces Bacteroidetes and increases in Firmicutes population, similar to what is seen in obesity. Increased ratio of Bacteroidetes to Firmicutes is linked with diminished body mass. *L. rhamnosus* and *Lactobacillus plantarum* are probacteria that convert dietary linoleic acid to conjugated linoleic acid (CLA). In mice, these bacteria prevent weight gain on a high fat diet. Various probiotic

strategies are being developed to tailor the GM in such a way that they can help reduce weight of the host. GM are also associated with low-grade inflammation and metabolic syndrome via endotoxemia [153].

4. **Viral infections.** Four animal (canine distemper virus, Rous-associated virus type 7, Borna disease virus, and SMAM-1) and three human viruses (adenovirus (Ad) 36, Ad-37, and Ad-5) are known to cause obesity [154]. Scrapie agent has been shown to produce obesity in mice [155]. The infection affects fat cell differentiation, modulates appetite, or cause inflammation that dysregulates the feeding centre of the brain [156]. SMAM-1 is an avian adenovirus that is associated with human obesity. The human viruses stimulate enzymes and transcription factors that cause differentiation of preadipocytes into mature adipocytes and accumulation of TAGs.

3.2.2 Obesogenic environment

1. **Sedentary lifestyle and neighborhood safety.** Rapid urbanization has brought about various energy-saving techniques that promote sedentary lifestyle: convenient and cheap motorized transport, elevators, household appliances, etc. Entertainment is available 24 x 7, on the television or the mobile phone. Instead of playing games in the fields, children and adults prefer to play video games on a comfortable couch. Built environment, especially in areas inhabited by people with low socioeconomic status, is devoid of safe parks and walkways. Often in unsafe neighborhoods parents prefer their children to stay at home rather than venture out in the parks. Physical inactivity results in reduced energy expenditure, and if calorie intake is not reduced, it will ultimately lead to weight gain [157, 158].

2. **Diet**. With the abundance of calorie-dense food in attractive flavors and affordable prices, calorie-intake has increased for many persons. Fast-food is available at nearby stalls and it has become easier to purchase ready-to-eat food rather than cook at home. With increase in the number of nuclear families and double-incomes, home-cooked meals have been replaced by take-aways, home deliveries, and restaurant dinners. Calorie, carbohydrate, fat, and salt intake has increased, while intake of fruits and vegetables has decreased. Sweetened beverages and alcohol add empty calories [159, 160].

3. **Socioeconomic status (SES).** In case of developed countries, the incidence of obesity decreases with increased income and education [161], as people enjoy food security, are aware of healthy choices, and can afford healthy lifestyles in socially secure neighborhoods. In developing countries, the situation is complex. Low SES is associated with lack of food and medicines, ignorance regarding health, hygiene, and family size, and unwillingness to change [162]. An increase in family income brings about weight gain that can exceed the healthy limit. This is promoted by food insecurity. High SES shows slight decrease in obesity, however, this may not hold true for obesity in children, as high purchasing power and lack of self-control may lead to splurging on unhealthy foods.

4. **Unhealthy food advertisements.** Many people, especially children, are susceptible to food advertisements [163]. Aggressive marketing of calorie-dense food, sweetened beverages, cereals, snacks, etc. on the television, in print, on hoardings, and in shops affects vulnerable people. The message is clear: eat to

feel good. Many adults, especially those prone to depression, are affected in the same manner as children. Children who are overweight or obese usually grow into adults with weight issues.

5. **Culture and Ethnicity.** Certain cultures prefer chubbiness in children and adults and consider it a sign of health [164]. In Asian cultures, hospitality and affection are demonstrated through food. Asian men and women are more prone to develop central obesity [165]. Reward eating also promotes intake of unrequired calories in the form of high fat/high sucrose foods.

6. **Endocrine Disrupting Chemicals (EDCs).** The endocrine disrupting chemicals are man-made chemicals that block connections between hormones and their receptors [166]. The number of EDCs in the environment is increasing rapidly, even though their use has been banned. Their role in obesity has been highlighted by Brown et al. [167], who have used the U.S. National Health and Nutrition Examination Survey data, collected over nearly 4 decades, showing increase in calorie intake and BMI over time. For a given amount of calorie and macronutrient intake and leisure-time physical activity, the predicted BMI was significantly higher in 2006 than in 1998, indicating that factors other than diet and physical activity are contributing to the weight gain.

   More than 800 EDCs have been identified [168]. Persistent organic pollutants (POPs) and certain heavy metals have been classified into EDCs, metabolism disrupting chemicals (MDCs), and mitochondrial function disrupting chemicals (MtDCs). They can interact with nuclear and mitochondrial genes and bring about epigenetic changes, decrease insulin sensitivity, promote inflammation and obesity, decrease basal metabolic rate (BMR), and narrow down the vasculature.

   EDCs may be classified into obesogens and diabetogens. The obesogens (e.g. tributyltin, bisphenol A, phthalates, and metals like arsenic) can increase adipocyte differentiation and adipose tissue depots, disrupt normal lipid metabolism leading to obesity. The compound atrazine inhibits the electron transport chain in the mitochondrion. It has been shown to decrease BMR. Diabetogens either destroy beta cells of pancreas or disrupt their function leading to diabetes [169]. Bisphenol A blocks insulin receptor site causing insulin resistance.

7. **Weight-gain caused by pharmacotherapy.** Certain drugs can lead to weight gain or redistribution of fat. Large increase in weight may be accompanied by dyslipidemia, insulin resistance, metabolic syndrome, and increased risk of type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), CVD, and cancer. Drugs associated with weight gain are described below.

a. **Antidepressants**. Drugs causing up to 5 kilogram per year weight gain include the following:

Tricyclic agents like amitriptyline and doxepine.
Selective serotonin reuptake inhibitors (SSRIs) like paroxetine and citalopram.
Serotonin and norepinephrine uptake inhibitors (SNRIs) like venlafaxine and duloxetine.
Monoamine oxidase inhibitors (MAOIs) like moclobemide, phenelzine.
Others like mirtazapine, mianserine, and maprotiline.
Bupropion is a norepinephrine and dopamine reuptake inhibitor that reduces food cravings. In US bupropion and naltrexone combination has been approved as an anti-obesity drug.

b. **Mood Stabilizer.** Lithium used in the treatment of bipolar disorders causes a weight gain of more than 5% of the initial body weight.

c. **Antipsychotics.** Typical antipsychotics like haloperidol and perphenazine cause weight gain of up to 5 kg/year. Some atypical antipsychotics like clozapine and olanzapine can cause more than 5 kilogram weight gain in a year (4.5–16.2 kg/year). Atypical antipsychotics like amisulpiride, quietapine, and sertindole cause weight gain of up to 5 kg/year.

d. **Anticonvulsants.** Topiramate and zonisamide produce weight loss. Gabapentine and pregabalin cause weight gain of up to 5 kg/year. Valproate and carbamazepine cause weight gain of more than 5 kg/year [170].

e. **Antihyperglycemics.** Type2 diabetes is strongly associated with diabetes. Many of the drugs used in the treatment can cause weight gain. Insulin, meglitinides, and sulfonylureas are known to cause weigh gain. Sulfonylureas like glimepiride, glyburide, glibenclamide, and gliclazide) and meglitinides (e.g. repaglinide) stimulate insulin secretion from the pancreas. Thiazolidinediones (TZD) or glitazones (e.g. pioglitazone) improve insulin sensitivity by acting on transcription factor PPAR-γ, which is involved in glucose and fat oxidation. Insulin increases lipogenesis and fat storage resulting in weight gain [171].

f. **Antihypertensives.** Weight gain is often associated with hypertension, and certain medicines used in the treatment of hypertension can cause weight gain. These include beta-blockers (atenolol, propranolol), angiotensin receptor blocker valsartan, and calcium channel blocker diltiazem [172].

g. **Corticosteroids.** Although short-term use of corticosteroids is not associated with significant change of weight, long-term use (> 3 months) is associated with significant gain of weight. Some patients showed a weight gain of >10 kg/year with prednisone [173].

Since many of the patients are already struggling with the problem of overweight or obesity, it is important to prescribe drugs that are weight neutral or promote weight loss.

4. Direction of future research

The obesity pandemic has spread across the globe and a lot of research is being done regarding its control. If the cause of obesity is known, it is easier to cure or limit the disease. Most of the current research is related to diagnosis of the underlying causes of the condition, as removal of the cause can ameliorate the condition. Suitable lifestyle changes and pharmacotherapies are being designed to reduce weight. Different types of surgical interventions have been improvised to stop weight gain/promote weight loss in patients with severe obesity.

5. Conclusion

Obesity prevalence is increasing worldwide to assume pandemic proportions. Since many diseases are associated with obesity, it is important to identify the presence and causes behind overweight and obesity. We have attempted to list the various causes behind obesity, but we may have missed out some inadvertently or due to lack

of space. The purpose behind this work is to generate awareness about how overweight and obesity are sometimes beyond the patient's control. People with obesity of all ages have to face discrimination in the society, teaching institutes, and at the workplace. Often this discrimination leads to depression, stress, and overeating and aggravates the problem. It is important to remove this stigma and to consider people who are having to deal with this stigma as victims, rather than justifying the discrimination.

The World Health Organization has recognized obesity as a disease. It is important for physicians and healthcare workers to treat patients with obesity with compassion and empathy, to be open to endogenous and exogenous causes of obesity, and to suggest weight loss remedies if the patient is unable to achieve it himself/herself.

Conflict of interest

The authors declare no conflict of interest.

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