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Sadia Hassan *Editors*

Dietary Phytochemicals

A Source of Novel Bioactive Compounds for the Treatment of Obesity, Cancer and Diabetes

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Preface

The proper understanding of the interplay between obesity, cancer, and diabetes and how to manage them is the main focus of this book. This book entitled *Dietary Phytochemicals – A Source of Novel Bioactive Compounds for the Treatment of Obesity, Cancer and Diabetes* is a collection of chapters that were collaboratively written by authors from key institutions across the globe. An effort was made to highlight the link between obesity, diabetes, and cancer and the potentials of functional phytochemicals for their prevention and treatment. In Part I, the etiology and pathophysiology of obesity, diabetes, and cancer were fully discussed. Also, the role of peptides and the link between insulin, obesity, and cancer were presented. In Part II, the functions and the sources of important dietary phytochemicals were presented. Special chapters were dedicated to MicroRNAs as targets of dietary phytochemicals and the potentials of phytochemicals for breast cancer treatment.

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Contents

Etiology of Obesity, Cancer, and Diabetes

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1 Introduction

Obesity is of public health concern globally. The prevalence of obesity is on a constant increase. The effects of this non-communicable disease on the overall health of affected individual is devastating. Obesity worsens the symptoms of several diseases such as osteoarthritis, cancer, type 2 diabetes mellitus (T2DM), cardiovascular disease, and psychological disturbances (Dixon, 2010), and, as a result, significantly contribute to economic burden worldwide (Anyanwu et al., 2020; Wang et al. 2011; Withrow and Alter 2011). Factors responsible for obesity include biological, behavioral, and environmental factors. Obesity has been associated with cancer and diabetes. Cancer can be broadly classified into three categories, namely, carcinomas, lymphomas, and sarcomas. Approximately 1 in 3 cancer deaths are due

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to high BMI, low intake of fruits and vegetables, coupled with sedentary lifestyle or lack of physical activities, tobacco addiction, and alcoholism. Diabetes mellitus is a pancreas disorder which results in high glucose levels in the blood. There are different biological, environmental, and behavioral factors which metabolically interact to potentiate these diseases in healthy individuals. Mitigating obesity, cancer, and diabetes, which are often caused by several factors, require comprehensive approach. This chapter presents the etiologies and risk factors of obesity, cancer, and diabetes.

2 Obesity

Obesity is considered a public health issue which require immediate control measures. To better understand the etiology of obesity, it is pertinent to understand its underlying causes, which include excessive calorie intake, insufficient physical activity or sedentary lifestyle, poor food choices, genetic factors, and so on. Proper understanding of the role of genetics in obesity is also very important (Pereira-Lancha et al., 2012). The prevalence of obesity is influenced by various socioeconomic, environmental, and behavioral factors which result in the accumulation of fats in the adipose tissue. Obesity is prevalent in both developing and developed countries with more than 500 million people affected globally. Primarily, obesity occurs when calorie intake is more than energy expenditure with resultant weight gain. Obesity can also develop from the interaction of genes with other biological and environmental factors, such as diet, and lifestyle.

The treatment of obesity is not as simple as the affected individuals may desire. Reduced metabolic rate and gradual increase in appetite due to increased activities of appetite-stimulating hormones may undermine the effort of conventional methods used in treating obesity (Hemmingsson 2014; Johansson et al. 2014).

However, prevention is an important and crucial strategy in the management of obesity. Identifying different risk factors of obesity and how these factors are linked up with each other is vital. Children between 1–5 years can also be overweight or

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obese (Cunningham et al., 2017; Cunningham et al., 2014; Matthews et al., 2017). If a person is overweight in childhood, obesity is highly likely in adolescence (Cunningham et al. 2017; Ward et al. 2017). Increasing awareness on the risk factors associated with infant overweight is critical to preventing obesity in adolescence (Baidal and Taveras 2012; Danese and Tan 2014).

The drastic increase in obesity in adolescents is mostly due to behavioral changes directly caused by overeating and consistent weight gain. Clinical studies have shown that depression in adulthood can lead to obesity in adults (Luppino et al. 2010; Wurtman and Wurtman 2015). Additionally, mood swings are also associated with adult obesity, including chronic anxiety, etc. (Dallman et al. 2005), severe premenstrual syndrome (late luteal phase dysphoric disorder; LLPDD), and post-traumatic stress syndromes (PTSD) (Kubzansky et al. 2014). The tendency of obesity linked with mood disorders may occur in patients receiving behavioral medicines and antidepressant (Arjona et al. 2004; Fava et al. 2000; Wurtman and Wurtman 2015). In this condition, drug gradually affects the patient's eating behavior in two ways; either (a) reduced satiety, leading to the urge to eat more, or (b) increased appetite for calorie-rich foods (Wurtman and Wurtman 2015). Both conditions can be drastic and ultimately lead to weight gain (Fava et al. 2000). Similarly, in the case of some psychotropic drugs, the physical activity of the patient is limited, leading to decreased burning of calories; and, is one of the main causes of weight gain in such patients (Paluska and Schwenk 2000). Other environmental and psychological factors that contribute to weight gain in depressed individuals, include unemployment, low income, low self-esteem, disturbance in relation, family issues, educational challenges, isolation, etc., all of which can lead to abnormal food consumption and/or intake of high-calorie foods (Wurtman and Wurtman 2015). Weight gain is not only observed in individuals treated with psychotropic drugs, it is also observed in the population with hormonal disturbance, excessive intake of supplementation, anxiety, medical condition, etc. (Gariepy et al. 2010).

2.1 Etiology of Obesity

Ingesting calories in excess more than the body needs results in the storage of extra calories in adipose tissue (O'Rahilly 2009). When energy intake is more than energy expenditure, the result is weight gain, which when consistent can lead to overweight (BMI within 25–30), followed by obesity (BMI of 30 and above). Multiple factors responsible for obesity, include biological, behavioral, and environmental factors, among others. These factors are responsible for energy storage and weight gain (Aldhoon-Hainerová et al. 2014; Apalasamy and Mohamed 2015; Rao et al. 2014). Energy is mainly stored due to calorie intake in the form of macronutrients, such as carbohydrate, protein, fat, and alcohol. Calories are utilized via three metabolic processes; (1) thermic effect of food (TEF) (2) physical activity in which calories are burned (3) resting (basal) metabolic rate. Approximately 8–10% energy is utilized in TEF (energy required to digest and metabolized food). Weight maintenance

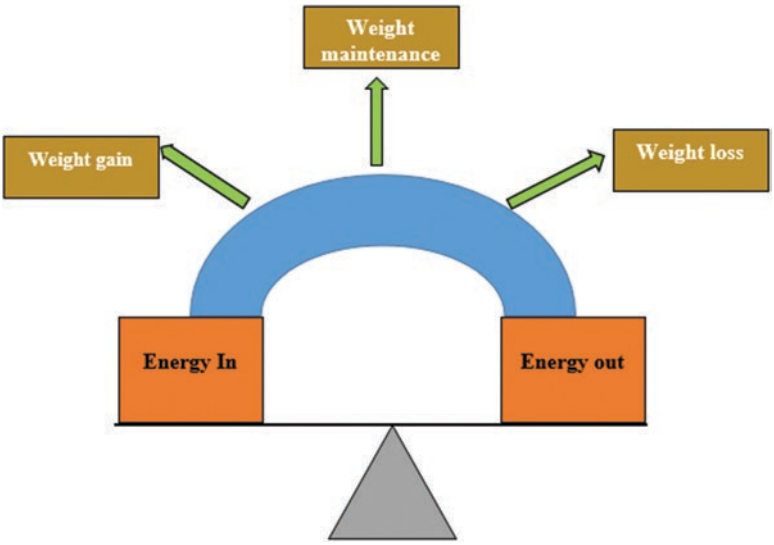

Fig. 1 Energy balance. Depicting an association between intake of food (Energy In) and the energy expenditure through the body during physical activity and metabolism (Energy Out)

is achieved when energy intake and energy expenditure are equal (Fig. 1). Changes in weight occur when energy intake is more than energy out or energy expenditure is more than energy intake. Both conditions lead to an imbalance in body weight. A healthy person become obese when energy intake is consistently more than energy expenditure for a prolonged period of time, usually months or years. Different factors such as genetic, environmental, and behavioral factors which directly contribute to high energy intake may result in weight gain (Fig. 2) (Hill et al. 2012).

2.2 Biological Factors

Biological factors associated with obesity include brain-gut axis, genetics, pregnancy, prenatal determinants, neuroendocrine conditions, menopause, medications, gut microbiome, physical disability, and viruses. If any of these factors is present and interacts with other factors (such as environmental and behavioral factors), it can lead to obesity.

2.2.1 Genetics

Most people with obesity have multiple genes which predisposes them to excessive weight gain. There is strong evidence that genetic makeup can contribute to the development of obesity. Studies on clones and adoptees showed that >70% of the

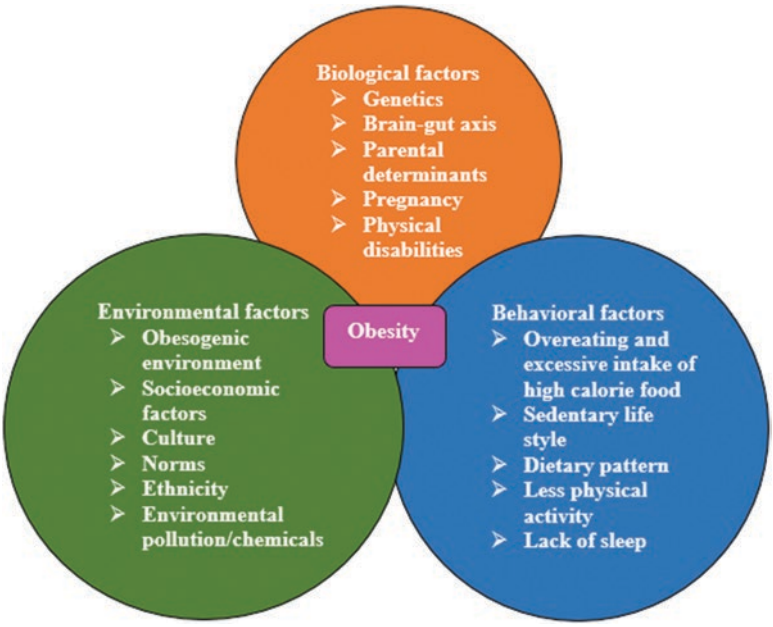

Fig. 2 Etiology of obesity

individual fat difference are due to genetic variations (Farooqi and O'rahilly 2008). Genetic obesity is associated with all aspects of energy homeostasis, including energy intake, physical activity, TEF, basal metabolic rate, food intake, etc. (Pereira-Lancha et al. 2012). The ob (Lep) gene that encodes the peptide leptin, and its alteration, causes obesity, and has been the main focus of researchers working on heritability of obesity (Zhang et al. 1994). Genetic studies of obesity showed that there are more than 300 genes and gene markers which are associated with obesity, and their interactions with environmental factors (Chagnon et al. 2003; Friedman 2003). There are 3 subgroups of genetic-induced obesity, including;

1. Monogenic obesity (due to single gene defect, e.g., leptin)
2. Syndromic obesity (chromosomal abnormalities, e.g., Prader-Willi syndrome)
3. Polygenic obesity (due to more than one gene variants) (Rao et al. 2014)

Monogenic Obesity

Monogenic obesity is caused by single gene mutation/variation. To date, several forms of early human obesity have been identified, which mostly occur due to gene mutation controlling the leptin-melanocortin path. This path regulates the intake of food. The genes responsible for this kind of obesity are listed in Table 1 (Farooqi and O'rahilly 2008; Rao et al. 2014). Continued efforts are made to identify and discover other potential candidate genes that are responsible for obesity in affected individuals.

Table 1 Genes associated with obesity

Gene	Encoded protein	Obesity expression	Cases identified
LEPR	Leptin receptor	Few days in life	2–3% of severe early-obesity
LEP	Leptin	Few days in life	<50 patient globally
MC4R	Melanocortin-4 receptor	Childhood	2–3% obesity in children and adults
SIM1	Single-minded 1	Childhood	<50 patient globally

Syndromic Obesity

Currently, at least 25 forms of syndromic obesity are known. Some of the most common syndromic obesity are; Bardet-Biedl syndrome, Prader-Willi syndrome, Alstrom syndrome, aniridia, genitourinary anomalies, Wilms tumor and mental retardation (Chung 2012). Prader-Willi is the most common syndromic obesity and a complex genetic disease caused by modifications in gene expression on the paternally inherited chromosome 15q11.2-q13 region. Under this syndrome, the affected individual is characterized by being obese, short stature, cognitive disability, excess food intake, and behavioral problems. Obesity is the main cause of morbidity and mortality among these sets of individuals (Angulo et al. 2015).

Polygenic Obesity

Genetic alteration with polygenic effects on energy intake is clinically significant, as this is the most vital human cases of obesity (Hinney et al. 2010). Some of the obesogenic traits arise partly due to the mutation in more than one genes. Polygenic variants are the alleles at different gene loci that collectively affect the heritage, quality, and quantity of the expression of phenotypes. The polygenic basis of obesity depends on individuals; every affected individual has a unique set of polygenic genes linked with the disease (Hinney et al. 2010). Genome-wide link and Metabochip studies showed single nucleotide polymorphisms with polygenic effects on body mass index. In meta-analysis of genome-wide link studies, as well as Metabochip studies, involving 339,224 individuals, 97 loci (new and previously identified) were found to be linked with BMI. The study demonstrated that these known loci are responsible for 2.7% of deviation in BMI (Robinson et al. 2015). Although, extensive research is still required to discover a wider range of susceptible loci that are present and associated with the environment in the expression of obesity (Rao et al. 2014).

2.2.2 Brain-gut Axis

The brain-gut axis (Fig. 3) regulates the utilization of food in response to homeostatic and non-homeostatic signals. In case of homeostatic (energy balance) system, the arcuate nucleus of hypothalamus integrates nutrient, neural, and hormonal

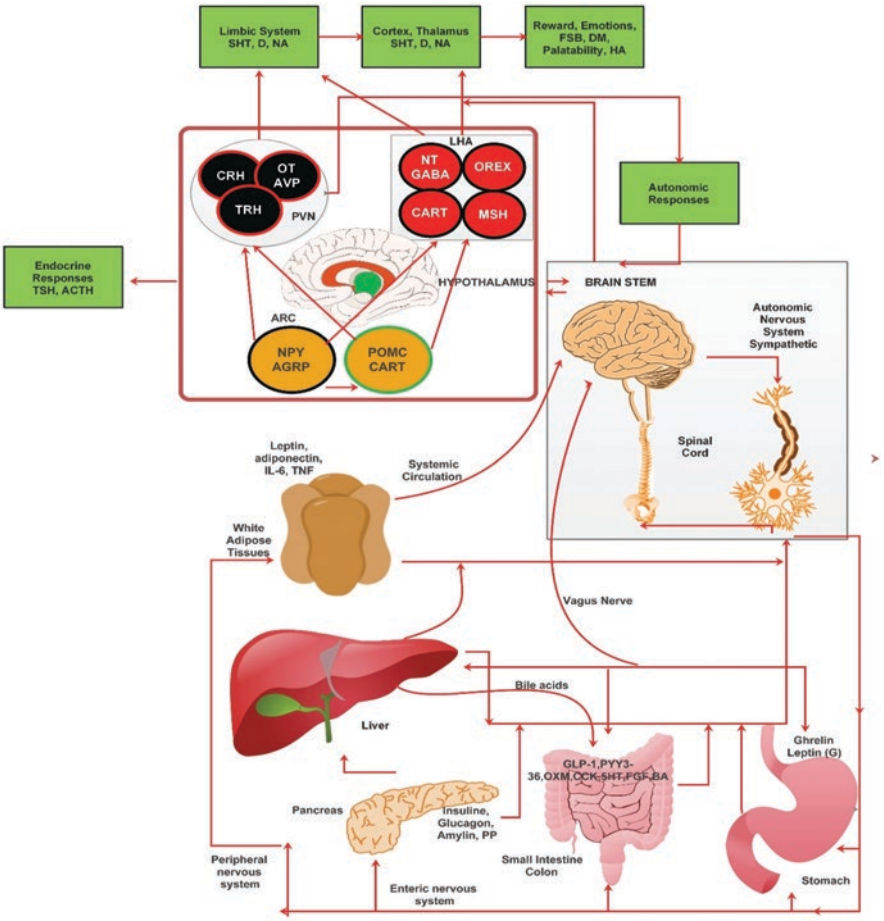

Fig. 3 Brain-gut axis and regulation of food intake

signals to regulate satiation, hunger, and satiety through higher cortical centers that control these signals to stimulate the sympathetic and parasympathetic nervous system, gastric function, and hormone secretion (Hussain and Bloom 2013). These signals are the means of communication between the brain, gastrointestinal system and adipose tissue. Individual characteristics associated with the brain, gastrointestinal system, and adipose tissue may cause variations in energy intake and storage among different individuals (French et al. 2012). The gastric function also affects hunger, satiation, and satiety. Similarly, the intake of food may also cause alterations in gastric function (Acosta and Camilleri 2014).

In case of obese individuals, there is difference in the brain-gut axis compared to healthy people. Obesity is directly related to higher fasting gastric volume, higher gastric emptying of solids and liquids, decreased satiation (a difference of 50 calories/5 kgm^{-2} of BMI), low level of satiation-linked hormone peptide YY (PYY)

(Acosta et al. 2015), lower levels of glucagon-like peptide-1 and cholecystokinin, higher levels of acyl-ghrelin (Sato et al. 2014), and increased levels of leptin with leptin resistance (receptor downregulation) (Myers et al. 2008). Furthermore, most of the biological etiologies of obesity disturb the brain-gut axis homeostasis. There is need to study whether change in brain gut-axis with intake of food is an effect or cause.

2.2.3 Prenatal Determinants

Several research have shown that nutritional and environmental factors during fetal and newborn life can permanently affect the functions and structure of many organs, which can lead to obesity. It has been noted that high pre-pregnancy and gestational weight can affect the body composition of newborn, which is the major cause of childhood obesity. Gestational diabetes is also associated with childhood overweight (Baptiste-Roberts et al. 2012). In addition, smoking during pregnancy appears to predispose the infant to excessive BMI and eventually weight gain. Interestingly, it has been observed that the method of childbirth may also increase the risk of obesity in offspring. Also, epidemiologic data suggest a direct relationship between newborn delivery and child adiposity. A systematic review and meta-analysis of 15 studies (approximately 163,796 participants) found a positive connection between childbirth and more BMI in adulthood (Darmasseelane et al. 2014).

2.2.4 Pregnancy

During pregnancy, weight gain is directly associated with fear of postpartum retention of excess weight. Different epidemiologic studies suggest that gestational weight gain is positively related to weight retention after pregnancy but not to a greater extent (Mannan et al. 2013). Studies have suggested that that the tendency of 2–3 kg weight gain and increase in waist-hip ratio after first pregnancy during 5 years is more as compared to non-pregnant women. After pregnancy, most of the women retained 4–5 kg, which often lead to obesity. A study conducted on 540 women, recorded their weight during pregnancy, after 6 months of pregnancy, and after10 years. The research showed that an average increase of 6.3 kg in weight from pre-pregnancy to follow-up (Rooney et al. 2005). Thus it is clear from the result that there is a positive correlation between pregnancy-induced weight gain and risk of obesity after pregnancy.

2.2.5 Menopause

Another important cause of obesity in women is menopause. According to a study conducted on American women, 48% of postmenopausal women (>50 years of age) are overweight and >25% are at high risk of obesity compared to premenopausal

women (Lambrinoudaki et al. 2010). Menopause is associated with changes in body composition and structure, such as accumulation of more fat mass, increased BMI, increased body weight, less physical activity, slow basal metabolic rate, and increased risk of other health disorders. Most of these conditions usually lead to less energy expenditure and, sometimes. Perimenopausal hormonal changes are directly linked with drastic increase in abdominal adiposity and more hip to waist ratio. Estrogen therapy may prevent these body composition changes and their associated metabolic consequences (Davis et al. 2012).

2.2.6 Physical Disability

Epidemiological studies showed that individuals with disabilities are at high risk of obesity compared to normal individuals. Individuals with disabilities are often unable to do physical activity and their body composition changes due to less energy expenditure. A study was conducted on the change of body composition in patients with acute spinal cord injury. Results showed a significant decrease in bone-mineral density and lean body mass during the first year of injury, due to less energy expenditure and increase in adiposity (Singh et al. 2014). One of the main causes of obesity in children is physical disability. The study also showed that children and teenagers with spastic quadriplegic cerebral palsy had a significantly low total energy expenditure and non-basal energy expenditure as compared to their healthy counterparts (Singh et al. 2014). It is conclusive to state that individuals with disabilities, either physically or mentally, are at high risk of developing obesity and other disorders.

2.2.7 Gut Microbiome

Different animals and human studies reported that gut microflora affects body weight by influencing energy metabolism and inflammation (Murphy et al. 2013). The human gut consists of 10–100 trillion microorganisms, indicating a 10-fold more microbial load compared to human cells in the human body (Cani and Delzenne 2011). Gut microflora breaks down large indigestible molecules into small digestible molecules and plays an important role in energy metabolism in the human body (Flint et al. 2012). In fact, the metabolites produce in the gut after fermentation of carbohydrates into simple sugar is important in metabolism. A study reported that gut microbiota isolated from an obese rat can transfer the obesity phenotype when transplanted into a germ-free rat. One of the advanced findings has seen in the diet-induced obese rat as well as the genetic mouse models of obesity, ob/ob and toll-like receptor 5 (TLR5) knockout mice (Vijay-Kumar et al. 2010). After that tremendous discoveries, it opens a new horizon for human studies to better understand the link between the gut microbiome and obesity in microbial diversity among obese and healthy individuals. However, bacterial species or genus also directly associated with obesity. There is need to further explore the microbial diversity in relation to obesity and energy expenditure.

2.3 Environmental Factors

The environment is one of the critical factors in the etiology of obesity. In most cases, biological factors interact with environmental factors to express obesity. These dynamics are required to be treated at first by endocrinologists, policy makers, and health practitioners involved in the treatment of obesity. Some of the major environmental determinants are discussed below.

2.3.1 Obesogenic Environment

Nowadays, food has been abundant and readily available for consumption. Most people eat food for pleasure and entertainment rather than for survival. The food industries and food supply chain make food readily available by creating a favorable environment for fast food, ready to drink beverages, and the foods rich in calories are among the major causes of weight gain (Bray 2014). Consequently, in this way, environment has become one of the major contributing factors in the development of obesity. Another cause of weight gain is modernization and the trend of fast food among the population. The new generation consumes a lot of fast and fried food items and alcoholic drinks that are considered one of the pillars of the obesogenic environment. Nowadays, these food supply chains attract their customers by providing different offers (such as buy one get one free) and celebrating different days (such as Mothers' Day, Fathers' Day, Independent Day, etc.). In this fast developing life, many people and families spend less time in the kitchen.

2.3.2 Socio-Economic Factors

There is an inverse relationship between socio-economic status and obesity all around the globe. This link is assumed to arise from the effects of society, status, gender, ethnicity, culture, economics, education, norms, etc. (Dubowitz et al., 2013). Each family has different traditions, culture, and foods. Culture consists of different beliefs, characteristics, and behaviors of different age groups, gender, society, and ethnicities that are followed by different families. Consequently, due to cultural variations, we have different norms and values that directly influence our dietary habits, health, and body weight.

Society directly affects a person's mental and physical health. Generally, it has been observed that obese individuals are immensely affected by stigma, biases, body shaming, and discrimination compared to healthy persons. The bias they usually face in their daily routine comes not only from society but also from their own family. All the discriminations received from the society influence his/her emotional and psychological behavior, and consequently affect his/her physical well-being. In our society today, overweight youth who encounter body shaming, disrespect, and

weight-based teasing are more prone to unhealthy eating, poor weight management, disturbed dietary lifestyle, binge eating, and minimum physical activity (Puhl and Brownell 2001).

2.3.3 Environmental Chemicals and Obesity

Nowadays, some of the alarming concerns are environmental pollution and the role of environmental chemicals in obesity. Different studies showed that certain endocrine-disrupting chemicals, or "obesogens," are potential risks to obesity. For example, phthalates are well-recognized obesogens, as they react with peroxisome proliferator-activated receptors (PPARs), which are responsible for the development of fat. There is need to investigate and identify more obesogens to prevent environmental health issues (Thayer et al. 2012).

2.4 Behavioral Factors

The behavioral factors are the monogenic factors or etiologies responsible for energy intake, less energy expenditure, overeating, etc. Individual choices and lifestyles essentially interplay between biological and environmental factors to express obesity. We are in an obesogenic food environment with foods in abundance, readily available, affordable, lots of variety, and convenience. In spite of all these conditions, the individual choice plays a major role in the consumption of food. Similarly, other behaviors, such as less physical activity, overeating, lifestyle, insufficient sleep, drinking habit, and smoking are self-inflicted behaviors that are not affected by the environment.

2.4.1 Increased Calorie Intake and Eating Habits

Currently, the trend of per capita consumption of refined cereal grains, sugar, and fats is dramatically increasing in form of processed, ready-to-eat fast foods, resulting in more calorie intake. Studies have demonstrated that diets high in carbohydrates and fat are linked with more energy intake. Mozaffarian et al. (2011) examined the relationship between lifestyle and change in weight in 3 groups of people (120,877 healthy women and men) over a period of 4 years. The results reported that weight gain was due to the consumption of potatoes, potatoes chips, sweetened beverages, unprocessed red meat, and processed foods, and less consumption of fruits, vegetables, whole grains, nuts, and yogurt (Mozaffarian et al. 2011). In other studies, it has been reported that excessive intake of liquid calories is a significant risk factor for the development of obesity. Studies showed that liquid beverages are rich sources of sugar, which is associated with high intake of calories and subsequent weight gain (Woodward-Lopez et al. 2011).

Another important issue is that weight gain is linked with eating patterns. Two eating disorders are linked with obesity: (1) night eating syndrome (NES) and (2) binge eating disorder (BED) (Beksinska et al. 2010). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), BED is defined as "frequent overeating in a short period of time marked by feelings of lack of control". On the other hand, NES is characterized by night eating, night snacking, eating after awakening from sleep, or more food consumption after having an evening meal. In studies exploring the relationship between NES and obesity, NES was reported as one of the major causes of obesity, such as increase in BMI due to more calorie intake at night with no physical activity (de Zwaan et al. 2014).

2.4.2 Sedentary Lifestyle and Less Physical Activity

Physical activity plays a vital role in maintaining personal fitness. It can constitute 20–30% of total energy expenditure per day. The energy expended during physical activity varies from person to person based on body shape, composition, structure, weight, lifestyle, dietary patterns, etc. Sedentary lifestyle such as sustained watching of TV, sitting at one place for a long time, using laptops, etc. are related to weight gain and obesity, despite exercise and diet (Hu 2003). Physiologically, a sedentary lifestyle constitutes less energy expenditure, thus promotes obesity due to reduced physical activity (Hamilton et al. 2007). There is an inverse relationship between physical activity and tendency to become obese. Many studies showed that physically active children are less likely to become overweight and obese in childhood and puberty, and have less chance to become obese in adulthood (Hills et al. 2011). Unfortunately, in this technological era, it is not rare for a person to spend all day in sitting position, with little or no physical activity (Hamilton et al. 2007). The situation is alarming because less physical activity leads to risks of several chronic disease, such as diabetes, cardiovascular diseases, and overall mortality. There is need to promote and spare at least 30 min per day for physical activity to control obesity and other health-related disorders (Fox and Hillsdon 2007).

2.4.3 Insufficient Sleep

In behavioral etiologies of obesity, another concerning factor related to modernization is insufficient sleep and exhaustion, usually due to night shift jobs, long working hours, extra work, entertainment, etc. Research findings strongly recommend sleeping at least 8 h per day to keep the mind and body healthy and active in both children and adults (Cappuccio et al. 2008). Research conducted on 12 healthy men observed the effect of sleep on their appetite and BMI. The subjects were kept 2 days without sleep and 2 days of sleep extension spaced 6 weeks apart with controlled physical activity and food intake. Results showed that sleep deprivation was linked with decrease in leptin and increase in ghrelin

associated with hunger and appetite. Epidemiological studies suggest that more food consumption and adiposity may contribute to insufficient sleep. Several studies have attempted to explain the association between insufficient sleep and weight gain.

2.4.4 Quitting Smoking

There is a concept that smoking cause weight reduction. Epidemiologic studies support this statement, with a study stating that 4–5 kg weight reduction was observed in smokers compared to nonsmokers (Audrain-McGovern and Benowitz 2011). Smokers usually gain weight when they withdraw from smoking. This weight gain may be due to nicotine withdrawal, increased food intake, and less energy expenditure (Filozof et al. 2004). Proper diet and adequate physical activity are helpful strategies for smokers planning to quit smoking.

3 Cancer

Cancer is a disease characterized by abnormal cell division, whereby the cell divides in an uncontrolled manner which eventually ends up with formation of a tumor (Saravanan et al., 2020). Further uncontrolled division results in the spread of the tumor, a process termed as metastases. The local or metastatic cancer causes suffering to the affected individuals, and may even cause death. There are various forms of cancer. This uncontrolled cell division can arise from any tissue or organ of the body. According to recent reports of World Health Organization (WHO), an estimated 9.6 million deaths were due to cancer in 2018, which makes cancer the second leading cause of deaths worldwide. This turns out that 1 in every 6 deaths is due to cancer. It has also been reported by WHO (2018) that approximately one third of cancer patients are due to five most important dietary and behavioral risk factors; including high body mass index (BMI), low fruits and vegetables consumption, sedentary life style, use of alcohol, and tobacco usage (Table 2).

Table 2 Prevalence of different cancers

S/No.	Cancer type	Number of cases (Millions)	Number of deaths
1.	Lung cancer	2.09	1.76 million
2.	Breast cancer	2.09	627,000
3.	Colorectal cancer	1.80	862,000
4.	Prostate cancer	1.28	–
5.	Skin cancer (non-melanoma)	1.04	–
6.	Stomach cancer	1.03	783,000

Source: (WHO 2018)

3.1 Major Types of Cancer

Cancer can be broadly classified into three categories, namely, carcinomas, lymphomas, and sarcomas.

1. **Carcinomas:** Carcinomas accounts for about 85% of the total cases diagnosed worldwide. Carcinomas develop in the cells/tissues of epithelial layers. It has four subcategories; adenocarcinomas (e.g. Lung Cancer), Squamous cell carcinomas (e.g. Oral Cancer), Transitional cell carcinoma (e.g. Bladder Cancer), and Basal cell carcinomas (e.g. Skin Cancer) (Vanita et al. 2011).
2. **Sarcomas**: The cancer which originates in the mesodermal tissues falls under the category of sarcomas (Lau et al. 2011). This category includes the tumors of bone, muscle, fat tissues, and hematopoietic tumors.
3. **Lymphomas**: This type of cancer accounts for about 9% of the total cases diagnosed in the world (Bali et al. 2010). As the name implies, lymphomas occur in the lymph cell of the human immune system. Individuals suffering from cancer caused by lymphomas has enlarged lymph nodes and modification of lumps. Lymph nodes are present in the lymphatic system of human body along with blood vessels of circulatory system (Bali et al. 2010).

3.2 Causes of Cancer

Technically it is a difficult task to find out the basic cause of any type of cancer. The reason behind this difficulty is that cancerous cells are actually affected by several cultural and extracellular microenvironment condition (Nagy 2011). However there are certain factors which have strong evidence in increasing the risks of cancer, including poor dietary habits, tobacco use, alcohol consumption, obesity, UV light, sedentary life style, and hereditary factors (López-Lázaro 2016). There are certain genes which act as tumor suppressors (e.g. BRCA1 and BRCA2); any mutation in these genes will be responsible for causing hereditary cancers, such as ovarian cancer, breast cancer, etc. (Kurioka et al. 2011). There are numerous studies which showed that there are high levels of mRNA in the tumors of metastatic stage, which can be cured with chemotherapy (Liu, 2010).

3.2.1 Diet and Physical Activity

According to the WHO, one of the most important factor accountable for cancer is diet. High BMI, less consumption of fruits and vegetables (low-energy-dense foods), lack of physical activity, tobacco use, and alcohol use are prominent risk factors, as they account for about one third cause of cancer deaths. Although, it has been estimated that around 30% of cancers are due to dietary factors in

industrialized regions, only a few definite relationships between specific nutrient-related factors and cancer have been established scientifically.

There is large research data which supports that overweight and obesity increase the risk of cancer, especially in esophagus, colorectal, breast in post-menopausal women, endometrium, and kidney, while high amount of alcohol consumption increases the risk of cancers such as esophagus, pharynx, oral cavity, larynx, breast, and liver cancers. Liver cancer has increased due to exposure to aflatoxins, while nasopharynx cancer is on the rise due to some types of fermented and salted fish. Risk of colon cancer can be reduced with physical activity. Similarly, there are other risk factors which probably cause different types of cancer. For example; colorectal cancer is associated with high intake of preserved meat; very hot drinks and spicy food leads to oral cavity, esophagus, and pharynx cancer; stomach cancer is probably due to salt and salt-preserved products.

Healthy eating patterns such as increased portions of fruit and vegetables in the diet are helpful against stomach, esophagus, colorectal, and oral cavity cancers. Healthy lifestyle that includes sufficient physical activity has been reported to be protective against breast cancer. The American Institute for Cancer Research (AICR) and World Cancer Research Fund (WCRF) state that high intake of fiber reduces the risk of colorectal cancer, while intake of red meat and processed meat increase the risk of colorectal cancer. The dietary recommendations to prevent cancers include high fiber foods and reduced intake of energy-dense foods, salted items and red meat (Fig. 4).

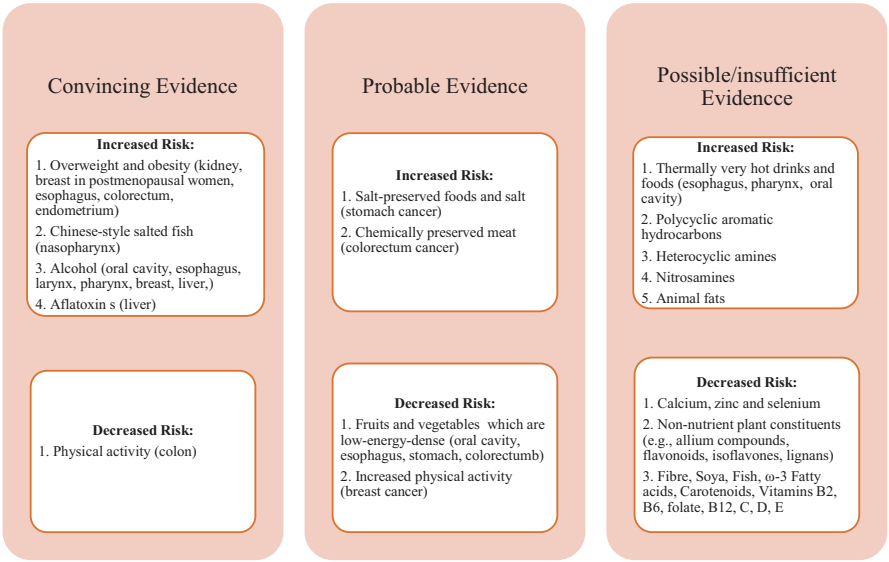

Fig. 4 Different risk factors for cancer

3.2.2 Use of Addictive Substances

The extensive use of tobacco is now recognized globally as a leading cause of different cancers and is currently estimated to account for 27% of cancer deaths (WHO 2018). Smoking tobacco increases the risk of developing many types of cancer such as cancers of the lung, larynx (voice box), mouth, throat, esophagus, kidney, stomach, pancreas, bladder, and cervix. The occurrence of lung cancer is about 20 times in chain smokers as compared to the nonsmokers (Furrukh 2013). However, nonsmoking individual who are exposed to secondhand smoke, termed as "Secondhand smokers", are also at risk of developing cancers due to the presence of tobacco smoke in the environment. However, many lung cancer cases have been reported in people who have never been smokers (Sun et al. 2007); many smokers never develop lung cancer.

Studies report that risk of developing prostate cancer is linked with the dose of alcohol being consumed by an individual (Fowke et al. 2015). All types of alcohol, including wine, beer, and spirits, increase cancer risk (Scheideler and Klein 2018). Alcohol increases the risk of seven types of cancers which includes highly prevalent cancers such as breast and bowel cancers (Corrao et al. 2004), along with being a major cause of liver cancer (Turati et al. 2014). Breast cancer risk is also relatively higher among those who consume relatively small amounts of alcohol (Seitz et al. 2012).

3.2.3 Sex and Reproductive Health

There has been strong correlation between male sex and occurrence of different types of cancers. Male sex is associated with not only male sex organ cancer, but also the prevalence of many non-sex organ cancer (Jones et al., 2011). It has also been reported that unsafe sex is a risk for certain cancers. The role of unsafe sex is indirect in causing different sexual organ cancers. Unsafe sex is a source of Human Papillioma Virus spread. This virus increases the risks of vulvar, vaginal, cervical, and anal cancers in its host (Weiderpass 2010; Vanita et al. 2011). However, further studies are needed to sufficiently establish the relationship between sex difference and occurrence of cancer.

3.2.4 Environmental Factors

Asbestos is a combination of certain minerals and is present in industrial and housing building materials. Mesothelioma is a malignant tumor formed on the lining of lungs, abdomen, and heart. There is a strong relationship between exposure to asbestos and development of mesothelioma (Reid et al. 2014). Benzene is a chemical found in gasoline, smoking, and pollution. According to American Cancer Society, people who are regularly exposed to high amount of benzene are at risk of developing cancers, such as acute lymphocytic leukemia

(ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma, and multiple myeloma. Skin cancer is often caused by exposure to the UV rays of the sun. Sunburn or a tan is actually the result of cell damage caused by the sun. Skin cancer can be prevented in most cases (Watson et al. 2016).

3.2.5 Genetics

Genetics is one of the key factors of cancer, and plays major role in cancer development. If there is any history of cancer in one's family, like breast carcinoma, taking extra precautions is significant. When cancer is genetic, a mutated gene can be passed down to the future descendants (Pomerantz and Freedman 2011). The metabolism of cancerous cells is controlled by several tumor suppressor genes and oncogenes. Any mutations in these genes can result in suppression or expression of metabolic enzymes which can develop cancer. Humans differ greatly with respect to their genetic makeup and similarly, as does the human populations of different regions; environmental factors are very much diverse around the globe. As a result, wide variation is seen in the prevalence of certain types of cancer in different regions. This can be illustrated by the risk of colon cancer and its associated mortality rate, which is different in various regions of Europe. Germany has reported the highest colon cancer cases and deaths, while, in comparison, Greece shows almost 50% less colon cancer cases and deaths (Carlberg et al. 2016). Of note is the epigenetic mechanisms of individuals which are more affected by the environmental factors, compared to genes. Several population based studies showed that migrant people are more prone to developing cancers which are highly prevalent in their host country (Carlberg et al. 2016).

4 Diabetes Mellitus

Diabetes mellitus is a pancreas disorder (an insulin producing gland) and results in high blood glucose level. The pancreas is located between the stomach and the spine, and plays a vital role in the process of digestion by releasing insulin into the blood (Diamond 2003; Wannamethee et al. 2001). Insulin is a hormone that regulates the blood glucose levels. Due to some physiological abnormalities, the release of this hormone may not function properly, leading to higher levels of glucose in the blood (Diamond 2003).

Diabetes mellitus is generally divided into four categories: type 1, type 2, gestational diabetes, and other categories of diabetes (Dungan et al. 2000). Type I diabetes may happen at any age. Type I diabetes happens because of autoimmune destruction of beta cells of pancreas. Many diabetes patients have markers of autoimmune destruction at the time of diagnose, comprising of antibodies of islet cells, tyrosine phosphatases IA-2, IA-2b, glutamic acid decarboxylase, and

insulin. In younger individuals, there tends to be a rapid rate of beta-cell destruction and development of ketoacidosis. Older individuals tend to have a more indolent course and later development of ketoacidosis, leading to that them often being labeled as having latent autoimmune diabetes (Opara and Dagogo-Jack 2019). Type 2 diabetes manifests as insulin resistance. In majority of the patients, initial plasma insulin concentration tends to increase, although insufficient to obtain glucose homeostasis due to insulin receptor resistance (Maina 2018). Over time, due to progressive failure of the beta-cell, absolute insulin deficiency tends to develop. A small number of patients diagnosed with type 2 diabetes will have severe insulinopenia with normal or near-normal insulin sensitivity at the time of diagnosis (Dungan et al. 2000).

Gestational diabetes occurs when glucose intolerance is identified during pregnancy. Diabetes can also be caused by other factors, including genetic defects, diseases of the exocrine pancreas, endocrinopathies, infections, and drugs (Dungan et al. 2000). The genetic defects include mature-onset diabetes of the young (MODY), which presents as impaired insulin secretion with little or no insulin resistance (Opara and Dagogo-Jack 2019). It can occur within the first 6 months of life (neonatal) and can be transient or permanent (Dungan et al. 2000). It can also occur at later age, although many exhibit mild hyperglycemia at early age. It has autosomal-dominant inheritance, with the varying natural history depending on the underlying genetic defect (Hasler et al. 1995). There are various genetic disorders that can involve mutations of the insulin receptor, leading to insulin resistance (Dungan et al. 2000). Additionally, there are several genetic disorders that could lead to diabetes whose mechanisms are still controversial (Opara and Dagogo-Jack 2019). Fibrotic changes to the pancreatic parenchyma, due to diseases such as cystic fibrosis or chronic pancreatitis, can lead to diabetes. In addition, diseases such as pancreatic cancer or pancreatic trauma can also lead to diabetes. In the presence of pre-existing failure of beta-cell, other endocrinopathies, such as cortisol, growth hormone, glucagon, and epinephrine, can exacerbate insulin resistance. Infectious disease, such as congenital rubella, can predispose individual to development of diabetes. Other infectious agents are thought to predispose individuals to diabetes (Hasler et al. 1995). Various drugs can also induce insulin resistance and impair beta-cell function (Dungan et al. 2000).

With such a disease as diabetes, it is imperative that patient learns about this illness and how to manage it. Such an undertaking is significant in ensuring that, in circumstances where diabetic patients experience complications from this disease and are not close to a hospital or a medically trained professional, they can respond to such situations in an effective manner. Diamond (2003) argues that, in such a case, the knowledge the diabetic patients have on diabetes might be the only thing that will save their life. It is also vital to note that diabetes is lifestyle illness and the routine or day-to-day undertakings of an individual with diabetes is of great concern, especially in relation to having adequate knowledge about this disease (Maina, 2018).

4.1 Causes of Type 1 Diabetes Mellitus

To realize the fundamentals of type I diabetes mellitus (T1DM), one needs to know the activities that lead to the establishment of this disease (Fig. 5). Hitherto, the etiology of diabetes have been classified into 3 categories, which include genetic susceptibility, viral, and environmental factors.

4.1.1 Genetic Susceptibility Factors

Type 1 diabetes mellitus can be hereditary. Epidemiological studies have revealed an elevated prevalence (6% in siblings, compared to 0.4% in common population) of T1DM among the families of T1DM patients due to genetic susceptibility (Pociot and McDermott 2002). The immunological studies of T1DM was developed on the hypothesis that insulin is known as non-self-substance in people suffering from T1DM. Therefore, it is rational to accept that either an impairment in insulin structure or in recognition site can be responsible for T1DM (Acharjee et al. 2013).

In mammals, each nucleated cell has distinct marker molecule that is expressed at the surface of each cell, which helps in cell identification. Major histocompatibility complex (MHC) is a group of genes responsible for the synthesis of these marker molecules (Willey et al. 2009). Human leukocyte antigen complex is responsible for the same task in human beings. Two chromosomal sections in the human species genome have presented with significant and consistent evidence of a link with T1DM. These including HLA at the insulin gene region at chromosome 11 and at chromosome 6. In this context, HLA genes are categorized into 3 distinct classes (class I, II, and III) according to the type of molecules they produced (Pociot and McDermott 2002).

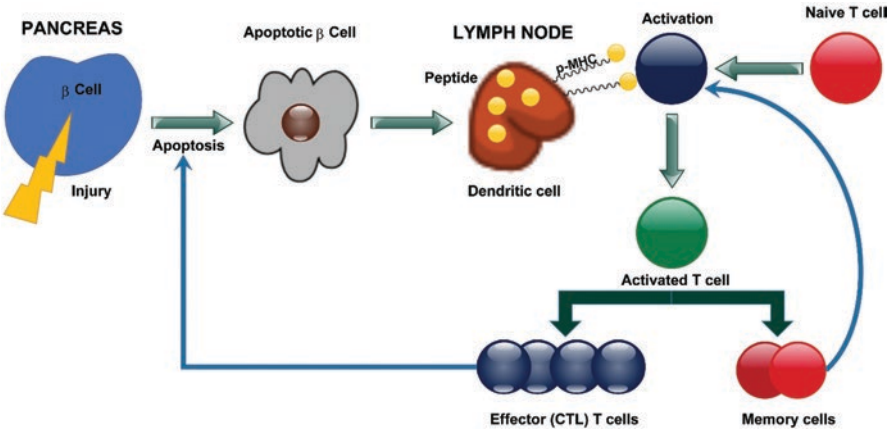

Fig. 5 Etiology of type I diabetes mellitus

Class I marker molecules are established at the surface of all nucleated cells and these cells are recognized as self. Class II molecules are found only on surface of particular cell that vigorously participate in body defense system including dendritic cells, epithelial cells, macrophages, and T cells. In T1DM, class II genes are of chief significance and can be further separated into 3 subclasses, which include HLA-DR, HLA-DP, and HLA-DQ. Several genetic studies have depicted that few variants of HLA-DR and DQ genes (HLA-DRB1, DQA1, and DQB1) take part in the genetic predisposition to T1DM. Amongst the HLA-DQ is a fierce vulnerability (Redondo and Concannon 2020). The insulin genetic region on chromosome 11 is the second significant genetic susceptibility for T1DM. Genetic studies on mice and humans have also shown the presence of insulin as autoantigen and antibody in the onset of T1DM (Pihoker et al. 2005). Some other chromosomal regions of human genome have also shown possible roles in onset of T1DM, such as interleukin-2-α- chain receptor (IL-2RA), protein tyrosine phosphatase non-receptor type 22 (PTPN-22), and cytotoxic T-lymphocyte antigen-4 (Espino-Paisán et al. 2009).

Recently, genome wide association studies have been applied to categorize genetic loci-associated T1DM. In addition to the traditional methods of evaluating chromosome, genome wide association studies analyze the whole genome for single nucleotide polymorphism (SNP). SNP frequently take place in T1DM patients, and usually linked to the disease. These SNPs are used to mark the vulnerability loci. By applying this technology, several susceptible loci were identified for T1DM, including BACH2, CD69, CD226, CCR5, CLEC16A, CI1QTNF6, CTSH, ERBB3, GLIS3, IFIH1, IL-2, IL-2RA, IL-7R, IL-10, IL-18RAP, IL-19, IL-20, IL-27, PRKCQ, and SH2B3 (Barrett et al. 2009; Cooper et al. 2012).

The occasional complex cascades that lead to T1DM have been streamlined in a model pattern developed by Mahaffy and Edelstein-Keshet (2007). The study pointed out that any impairment of insulin producing β-cells can initiate the onset and the triggering of T cells against self-antigens of the human body system. The impaired β-cells undergo apoptosis which make self-antigen with short peptides. In the pancreatic lymph nodes, these peptides are present on the antigen presenting dendritic cells. The native T cells, when in contact with these kind of antigens, are unable to recognize this as self-system protein and usually get discriminated, resulting in the identification of these substances as foreign antigens. A portion of discriminated T cells persist as memory cells, while other fractions actively take part in the cell apoptosis, leading to T1DM (Acharjee et al. 2013).

4.1.2 Virus-Related Contagions

Studies have shown the association of T1DM with different strains of enteroviruses. Coxsackie virus B-4 has a protein 2C identical to the glutamic-acid-decarboxylase enzyme, which is present on the islets of Langerhans. Due to molecular simulation, protein 2C erroneously assemble as a self-molecule, thus not confronted by the T lymphocytes. Generally, T cells attack the protein envelope, including VP1, VP2,