Emerging Contaminants and Associated Treatment Technologies

Muhammad Sajid Hamid Akash
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Endocrine Disrupting Chemicals-induced Metabolic Disorders and Treatment Strategies

Springer

Emerging Contaminants and Associated Treatment Technologies

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This book is dedicated
To
My Beloved and Adorable Little Twinkles
Muhammad Aqdas Akash
&
Zainab Akash

Foreword

I am delighted to write the foreword for "*Endocrine disrupting chemicals-induced metabolic disorders and treatment strategies*" The editors; Dr. Akash, Dr. Rehman and Dr. Hashmi have met the need of our research society by compiling the basics through the advances. Although this book undoubtedly justifies having an extensive readership, it should be more professionally read by researchers in the field and specialists of endocrinology with expertise in clinical practice. Rather truthfully, this book has been edited by the authors, other than whom no one else could have probably written it in this way.

Dr. Akash and accompanied editors of this book have excelled in the field of metabolic diseases and environmental pollutants and their impact on health. This book highlights the role of endocrine disrupting chemicals in inducing, progressing and/or prevailing metabolic disorders. The different segments that this book serves including endocrine physiology, intro to endocrine disruptors and their association with metabolic disorders, contributes to the endocrine science. Dr. Akash and his able companion editors have sensibly provided the updated art and science of endocrine physiology particularly involved or "at risk" for metabolic disorders on exposure to endocrine disruptors. Moreover, they have also focused wisely on these factors relating to their sources of exposure and mechanism of pathogenesis. Most interestingly they have also provided the probable preventive as well as treatment approaches for these endocrine disrupting chemicals induced metabolic disorders. These categorical discussions in the book represent the staircase evolutionary approach for taking the basics of metabolic disorders and understanding of endocrine disrupting chemicals to the development of metabolic diseases. This is followed by the probable intervention which suggests possible preventive and curative measures. This unique compiling effort gives an affirmative sign to be the hallmark for the success of this book in future.

In addition, this book not only serves as a source of providing major endocrine disruptors and metabolic disorders on a single platform to researchers, but is designed to also serve as a companion resource to clinicians, including endocrinologists. It may also assist the educational basis for many post graduate students enrolled or preparing for admissions in similar disciplines like Medicine, Pharmacy,

Nursing, Gastroenterology, and Endocrinology. I would like to mention here that this is a valuable work done by Dr. Akash and team for providing each chapter with evidence-based background material highlighting principal science, envisioned not only for the professional who already possesses a basic understanding of the principles of endocrinology and associated diseases but also for early stage researchers.

It is my expectation and belief that this book will deliver an effective knowledge and understanding based on practical work done so far for researchers and professionals considerate for patient care to help reduce the exposure to endocrine disruptors and improve incidences of associated metabolic disorders. I believe that "*Endocrine disrupting chemicals-induced metabolic disorders and treatment strategies*" will stand as one of the opening cornerstones as so far, no book has been published that provides the comprehensive compilation of what this book depicts relating endocrine disruptors and metabolic disorders. I wish this book had been available countless years ago!

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Foreword

Endocrine Disrupting Chemicals-Induced Metabolic Disorders

We live in a world surrounded by environmental pollutants and toxicants, including endocrine-disrupting chemicals (EDCs) which pose a significant health risk to current and future generations of humans and animals alike. Some of these EDCs are understudied or, even more frightening, undiscovered. Other chemicals currently deemed safe may be dangerous, and their adverse outcomes are not yet measurable. Therefore, high-quality research and publications are necessary to raise awareness and guide scientists, policymakers, and the public.

This book introduces the normal and maladaptive processes of the endocrine system, glands, and associated disorders, including EDCs-induced metabolic ones. The essential material detailed within is the preventive and intervention treatment strategies potential in combating these illnesses. The many authors of these different chapters have contributed to highlighting the therapeutic impact of these bioactive compounds, further adding to this work's importance and educational value.

Enduring damaging effects of EDCs is something that will arouse interest in readers, herein debating hot topics from alterations in the gut microbiota to enhanced antibiotic resistance. Discussion to positive lifestyle changes in metabolic disorders are given relating to intermittent fasting and some bioactive compounds present in food, is of interest to the layperson. This may reveal candidate targets for pharmaceutical drug development, as responsivity is needed to fight our widening obesity pandemic.

The dual basic/clinical nature of this book allows researchers from both ends of the spectrum to read and learn. Providing knowledge and understanding based on studies thus far allows this book to act as a companion resource for both undergraduate and post-graduate students in the Health Sciences.

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Preface

Metabolic disorders (MDs) are promptly aggregating in the increasing population globally. This is greatly affecting the social and financial status of individuals particularly of developing and/or underdeveloped countries. Unfortunately, specifically these countries are also victims of environmental contaminants and habitual impurities that can be considered as the foremost keystones not only for initiating the occurrence but also for flourishing the progress of MDs. These contaminants include a major contribution of endocrine-disrupting chemicals (EDCs). According to the World Health Organization (WHO), these EDCs are "mostly *man-made, found in various materials such as pesticides, metals, additives or contaminants in food, and personal care products*" and that "Human exposure to EDCs occurs via ingestion of food, dust, and water, via inhalation of gases and particles in the air, and through the skin." This accentuates the urge to better comprehend the principal disease mechanisms, which will not only help in eradicating these underpinning causative factors but may also propose targeted therapy for the MDs caused by EDCs.

This book entitled "Endocrine-Disrupting Chemicals-induced Metabolic Disorders and Treatment Strategies" is envisioned to first provide an introduction to the endocrine system and MDs followed by a profound discussion on the role of various EDCs and/or sources of EDCs in causing the induction, prevalence, and even progression of MDs. Lastly, in the third part of this book, we have deliberated the potential account of prevention and therapeutic intervention by elaborating the treatment strategies of EDCs-induced metabolic disorders.

We considered writing this book as till now, there is no such comprehensive text available in a compiled book format that can actually provide the broad notion of EDCs-induced MDs under one roof in a co-jointed manner. Nevertheless, existing books on the said topic seem to be presented in a fragmented way limited to the introduction of either endocrine or MDs. They deliver more like a repetition of basic endocrinology rather than a rational staircase compiling the physiology of the endocrine system and related metabolic disorders which comprehensively provide endocrine gland's physiology; moreover, we have also discussed in detail all the associated endocrine metabolic disorders, i.e. hyperthyroidism, hypothyroidism, iodine deficiency, hypoparathyroidism, adrenal insufficiency, Cushing's syndrome,

acromegaly, galactorrhea, erectile dysfunction, central diabetes insipidus, hypopituitarism, pituitary apoplexy, and diabetes mellitus. Further, we have included the deficiency of some enzymes which are involved in the normal metabolic pathways of carbohydrates like fructose, galactose, and glycogen. They are mostly autosomal recessive disorders that occur extensively in MDs. Similarly, impaired lipid metabolism and thyroid function along with mitochondrial dysfunction, inherited metabolic disorders have also been expanded in great detail with their direct and/or indirect association for inducing and progressing MDs.

We felt the presence of a huge gap existing among the fundamentals of endocrinology, induction of MDs, and role of EDCs in inducing MDs in the text of available books on the topic, for which everyone needs to hop between the explanation of elementary perceptions of the endocrine system and the description of associated disorders occurring due to any dysfunction in the system. Therefore, we have tried our best to relate each vital component of the endocrine system as depicted above for proper body regulation as well as its dysfunction for induction of MDs.

Another addition to the valuable totaling of this book is a description of occurrence and exposure of endocrine-disrupting chemicals to the human being which include but are not limited to polychlorinated biphenyls for electronics, paints and floor coats, fire retardants used in furniture and textiles, phthalates used in plastics and scents, parabens used for the protection of products such as lotions and sunscreens, and alkylphenols used in detergents and pesticide formulation. The increased accumulating evidence of EDCs in our environment includes persistent organic pollutants, bisphenol A, and phthalates that illustrate their important role in the occurrence of metabolic diseases (obesity, T2DM, and metabolic syndrome). One of the noteworthy public health apprehensions of these EDCs is their enduring damaging effects. The role and influence of endocrine disruptors and their link to the ecosystem and human health have already been deeply covered over several years. However, several questions arise about the mechanisms of action of the EDCs, and further research is required. In this book, we have given the current understanding of the probable health dangers of EDCs in humans which highlight a requisite for increasing awareness of EDCs exposure and their enduring damaging health effects. Why we are talking about these “enduring damaging health effects” with great emphasis here? The answer to this is these EDCs-induced MDs are becoming a big source for antibiotic resistance. Yes! Some pathogens are also becoming resistant to the use of antibiotics to treat infections that are associated with EDCs-induced metabolic disorders. Besides, gut microbiota become altered because of EDCs-induced metabolic disorders. So we have also provided information on how EDCs can influence the gut microbiome and finally lead to the development of MDs. Other EDCs that have been taken into account for inducing MDs which are included in this book, including polychlorinated biphenyls (aromatic hexagonal biphenyl compounds), furans (an EDCs found in processed food, industrial process, pharmaceutical products, and smoke), heavy metals (such as cadmium and arsenic), flame-retardants (fire extinguisher such as halogenated, organophosphosphate, nitrogenous, inorganic, and intumescent coatings), phthalates, pesticides, perfluoroalkyl substances, polycyclic aromatic hydrocarbons, tobacco, pharmaceu-

tical products waste, and parabens. As we also have laboratory experience working on some of these EDCs to experimentally explore the mechanistic details of them by inducing pathological alteration and causing diseases like hepatotoxicity, mutagenicity, nephrotoxicity, genotoxicity, teratogenicity, and immunotoxicity, we also felt the potential urge for exposing the roles of bisphenol A (a toxic, mutagenic, carcinogenic, and endocrine disruptor) and aflatoxins (substituted bisfuranocoumarins, a secondary fungal metabolite).

We think that this communal etiology we have so far provided from the introduction of endocrinology till the dysfunction and occurrence of MDs with a potential role of EDCs can significantly support the need for a better understanding of these dysfunctions to reveal unusual therapeutic targets for the development of pharmaceutical drugs. This can be achieved by utilizing nanotechnology, a rapidly flourishing field that has emerged as cutting-edge technology in the twenty-first century indicating a promising future. Therefore, we are successful in showing how such novel technologies along with other therapeutic candidate molecules or techniques and/or preventive methods can ameliorate the hazardous effects of EDCs that occur in the form of induction and prevalence of MDs. The most important ones that we have discussed here, though certainly not the only ones, are the roles of nanoparticles in the management of metabolic disorders, intermittent fasting, herbs, and spices as a natural medicine for MDs. Similarly, bioactive compounds like polyphenols, phytosterols, carotenoids, prebiotics, vitamins, and flavonoids can effectively be used in treating EDCs-induced diabetes mellitus, hypertension, obesity, hyperlipidemia, and non-alcoholic fatty liver disease.

The chapters given in this book actually depict a comprehensive view into the rising areas of research in the pathobiology of EDCs-induced MDs. This book also includes in-depth assessments on a variety of therapeutic targets of the endocrine system that can be either focused on reverting the MDs or preventing enduring damage to bypass the occurrence and/or progression of MDs. We are confident that the contents of this book will motivate and encourage not only the challenging deliberations but will also instigate innovative paths of research to further widen the information, awareness, and responsiveness towards pathogenic EDCs with the eventual objective of rendering this information provided in this book into therapeutic novelties.

Faisalabad, Pakistan — Muhammad Sajid Hamid Akash
Faisalabad, Pakistan — Kanwal Rehman
Islamabad, Pakistan — Muhammad Zaffar Hashmi

Acknowledgement

The editors would like to express their warm thanks especially to the authors of every chapter in this book who supported us and cooperated with us at every point and without whom it would have been impossible to accomplish this task. It is wholeheartedly expressed that the contribution of each author proved to be a milestone in the accomplishment of our end goal.

The support and the technical contribution of "Higher Education Commission" (HEC) of Pakistan are highly appreciable. Without their provision and funding, it would have been impossible to reach the objective. The credit for the accomplishment of this work goes to the research grants (21-667/SRGP/R&D/HEC/2016, 21-1061/SRGP/R&D/HEC/2016, 5661/Punjab/RPU/R&D/HEC/2016, 6429/Punjab/NRPU/R&D/HEC/2016, and 8365/Punjab/RPU/R&D/HEC/2017) awarded by HEC to the editors of this book, as these projects and their outcomes have provided us the importance and significant health consequences of environmental pollutants/toxicants including heavy metals and endocrine-disrupting chemicals (EDCs). These projects have helped us to determine the positive relation of diabetic parameters with heavy metal exposure and influence on antioxidant status (Project# 21-667/SRGP/R&D/HEC/2016); they have also helped us to explore the new pathways and factors like smoking involved in the pathogenesis of metabolic disorders like diabetes and obesity and extent of at-risk patients in our community (Project# 6429/Punjab/NRPU/R&D/HEC/2016). Similarly, the sources for EDCs exposure and introduction of the cost-effective treatment for EDCs-induced metabolic disturbance have been also focused (Project#5661/Punjab/RPU/R&D/HEC/2016, 6429/Punjab/NRPU/R&D/HEC/2016, and 8365/Punjab/RPU/R&D/HEC/2017). Nevertheless, gender differences have also been identified to influence the inflammatory biomarkers of insulin resistance in diabetes mellitus (Project#21-1061/SRGP/R&D/HEC/2016).

Interestingly, as in this book, many chapters have also highlighted the therapeutic impact of bioactive compounds to be a cutting-edge treatment approach for many metabolic diseases caused by EDCs. This reflects the positive work done by the editors of this book under HEC-funded projects for which the editors are highly indebted to, as this funding proved to be a landmark effort towards the success of the project.

In the end, we editors, wholeheartedly wish to recognize the valuable words written by Dr. Shuqing Chen, Professor of Biochemistry and Molecular Biology, Department of Precision Medicine and Biopharmaceuticals, College of Pharmaceutical Sciences, Zhejiang University, China and Dr. Ciarán Martin Fitzpatrick, Editor-in-Chief, BMC Endocrine Disorders and Department of Drug Design and Pharmacology, University of Copenhagen, Denmark for their tiring efforts done to accomplish this book.

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Part I
Introduction to Endocrine System and Metabolic Disorders

Chapter 1
Physiology of Endocrine System and Related Metabolic Disorders

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Abstract Endocrine system is comprised of multiple glands. All of these glands secrete different hormones into the body. Most of the body's functions, i.e., metabolism, growth, development, electrolyte balance, and reproduction, are regulated by these endocrine hormones. Numerous releasing and inhibitory hormones are secreted by the hypothalamus which eventually stimulates the pituitary gland's hormonal secretions. Some of these pituitary hormones act directly on the target organs, while others act on organs situated in different regions of the body. Pituitary gland secretes growth hormone (GH), thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), adrenocorticotropic hormone (ACTH), antidiuretic hormone (ADH), prolactin, and oxytocin. Other endocrine glands include thyroid gland (secreting thyroid hormone T3 and T4, calcitonin), parathyroid gland (secreting parathyroid hormone), adrenal gland (secreting catecholamines, mineralocorticoids, glucocorticoids, androgens, and cortisol), pancreas (secreting insulin and glucagon), gonads (secreting sex hormones), pineal gland (secreting melatonin), and thymus gland (secreting thymosin hormone). Most of the endocrine hormones are regulated by negative feedback mechanism. There are many metabolic disorders associated with the over and under production of all these hormonal secretions by different glands. In this chapter along with describing endo-

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crine gland's physiology, we have discussed in detail all the associated endocrine metabolic disorders, i.e., hyperthyroidism, hypothyroidism, iodine deficiency, hypoparathyroidism, adrenal insufficiency, Cushing's syndrome, acromegaly, galactorrhea, erectile dysfunction, central diabetes insipidus, hypopituitarism, pituitary apoplexy, diabetes mellitus, hypoglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic nonketotic coma.

Keywords Endocrine system · Physiology · Glands · Hormones · Metabolic disorders

Introduction

The endocrine system is a system that controls the release of chemical/physiological messenger called hormones from ductless glands in particular organs. Hormones play a role as "messengers" and are transported via blood into diverse cells of the body that deduce and perform action on this information. A small chemical that can enter the bloodstream and exerts its effect at a distant site in the body seems to be an incredible idea. However, this happens in our bodies every day in our life. These hormonal secretions in the body are responsible to act on received stimuli and maintain homeostasis. The vital functions of the body, i.e., growth, offspring production, maintenance of constant temperature, and the ability to perform basic functions and activities, are not possible without these hormones [1].

The endocrine system offers an electrochemical connection from the cerebral hypothalamus to all relevant parts of the body that involve in controlling of metabolism, development, reproduction as well as in growth. Two kinds of endocrine hormones exist, i.e., (1) steroidal (2) non-steroidal (protein based). Except child birth (special situation), endocrine system has a negative feedback check on all the hormones. If there is an increased activity related to a particular hormone, as a feedback action its activity is eventually decreased. There are other factors and also immune system is involved in maintenance of constant hormonal level [1].

Endocrine Glands and Respective Hormones

Glands are structures that synthesize and secrete chemical substances. There are two types of glands either exocrine or endocrine. Exocrine glands secrete their secretions outside the body like tears and sweat or inside a body cavity, e.g., Digestive pancreatic as well as salivary enzymes. While endocrine glands secrete their hormones directly into the bloodstream. These hormones travel and bind to specific receptors on the target tissue or organ and exert their effect. This specialized

system of endocrine glands and their hormones is collectively known as endocrine system [2].

The main endocrine glands comprise adrenal gland, thyroid gland, parathyroid gland, pituitary gland, gonads (ovaries and testes), and pancreas as illustrated well in Fig. 1.1. The hormones secreted by such glands involve in controlling of growth, metabolism, homeostasis, reproduction as well as development via transferring information straight to receptors situated on their corresponding or relevant organs of the body. A composite feedback loop scheme works in coordination to uphold a balance among all hormone levels [3].

Hormone concentration or amount of its secretion can be regulated by positive or negative feedback mechanisms. An increase in specific hormone levels inhibits secretion, and a decrease in specific hormone levels stimulates secretion. Pituitary gland (Fig. 1.2) is frequently mentioned to as the "master gland" as secretions of this gland coordinate the activities of additional ductless glands of endocrine system [2]. The hypothalamus is positioned right at the uppermost of pituitary gland and is portion of the brain that controls functions like observing the physical condition and maintaining homeostasis of body. The hypothalamus comprises numerous control centers that control emotions as well as various physiological actions. This one is the most important connections among nervous system as well as endocrine system [4] (Table 1.1).

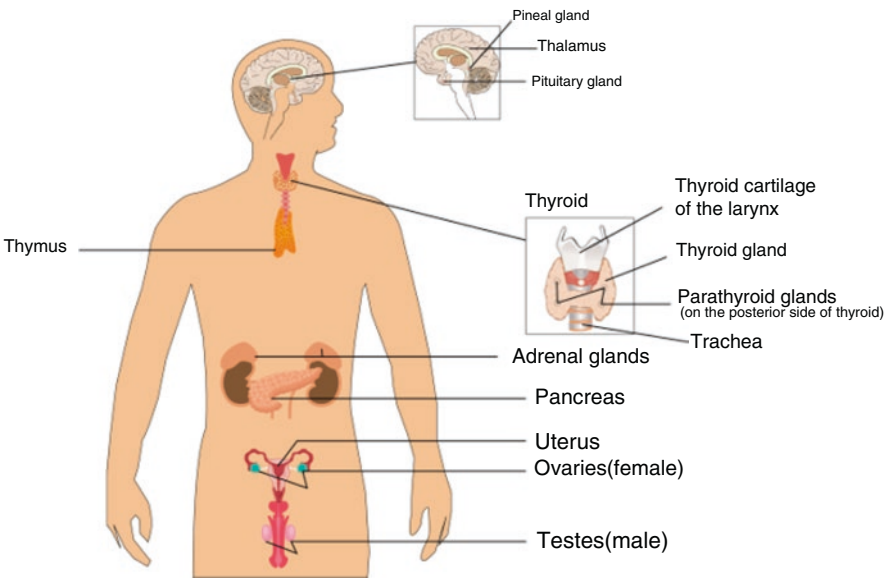

Fig. 1.1 An illustration of the location of various endocrine glands present in the human body. Figure adapted from after some modifications (www.physio-pedia.com, 2019)

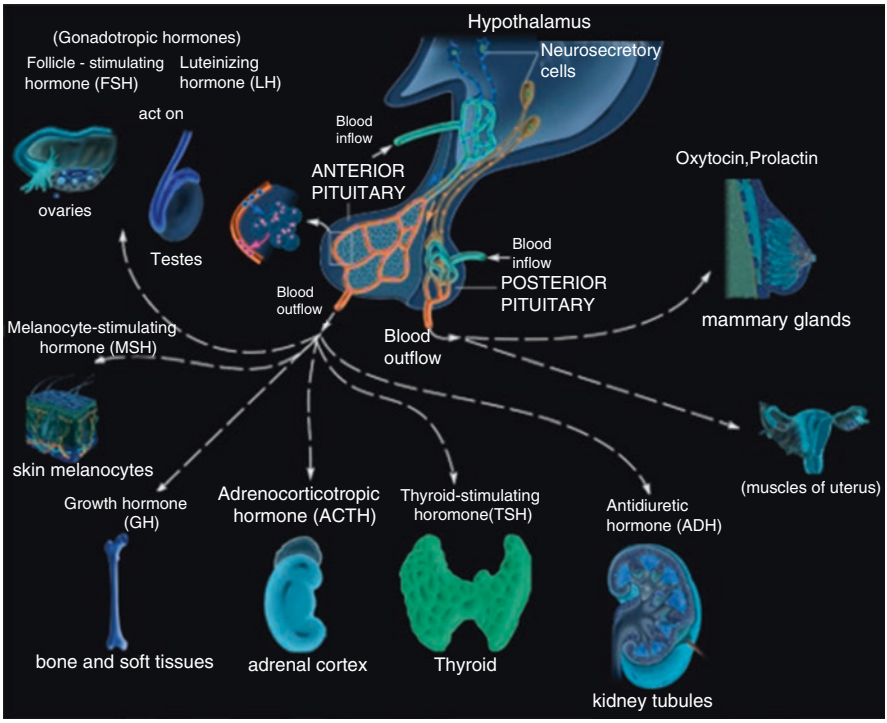

Fig. 1.2 Illustration of different endocrine glands and their hormones. Adapted from Abrahamson and Mosesso [2]

Table 1.1 Types of glands

Endocrine glands	Exocrine glands
These are the type of glands which do not possess any duct and secrete their hormones directly into blood or interstitial fluid	These are the type of glands that release their hormones through the duct, and these ducts are evacuated to the outside or inside of the organ's lumen
For example, Adrenal gland, pituitary gland, thyroid gland, parathyroid gland, and gonads and pancreas	For example, Pancreatic glands, mammary glands, sweat and salivary glands, they are excluded from the endocrine system

Pituitary Gland

Hypothalamus constitutes the inferior part of diencephalons; in addition, it is present directly above the brainstem. The pituitary gland is connected by a slender stem (infundibulum) to the bottom of the hypothalamus. There are two regions, i.e., (a) the anterior pituitary gland (anterior lobe or adenohypophysis) (b) the posterior pituitary gland (neurohypophysis or posterior lobe). Hypothalamus involves in

controlling of all secretions of pituitary gland together with various internal processes [5]. After receiving signals from systemic receptors, hypothalamus controls the physical and chemical characteristics of the blood such as blood pressure, nutrition, temperature, and water content. Whenever there is alteration in the homeostatic function or some other developmental alterations are needed, a cellular activity is induced by hypothalamus in desired body areas by stimulating release of pituitary hormones. Stimuli or signals from approximately entire areas/parts of nervous system are received by hypothalamus that is itself negatively controlled by pituitary regulatory hormones [1, 5].

Anterior Pituitary Gland's Hormones

Growth Hormone

Release of growth hormones from anterior pituitary is being controlled by hypothalamus. Hypothalamus secretes both inhibitory hormone [growth hormone releasing inhibitor (GHRIH) or somatostatin] and secretary hormone [growth hormone releasing hormone (GHRH)] into the hypothalamohypophyseal portal system. Both IGF-1 and GH negatively respond to pituitary gland and hypothalamus [6]. Negative feedback regulatory mechanism of hormones regulated by frontal lobe of pituitary gland is illustrated in Fig. 1.3. The stimuli which increase the growth hormone secretion are categorized as:

- Elevated quantities of peculiar amino acids (A.A) in plasma
- Hypoglycemia and fasting
- Stressful/distressing stimuli

The secretion of growth hormone (GH) decreases with increasing levels of glucose, cortisol, and free fatty acids (FFA) in the plasma as well as during rapid eye movement sleep. The main functions of GH include the following:

- It stimulates the growth of bone, cartilage, and soft tissue by the action of IGF-1 (insulin-like growth factor or formerly known as hormone C). Its secretion in the liver, kidney, and other tissues is increased in response to GH.
- It stimulates the mobilization of fat by releasing fatty acids from adipose tissue.
- It increases the rate of protein synthesis in all body cells.
- Hepatic glucose output is increased by GH.
- The rate of glucose consumption is reduced all over the body due to reduced uptake of glucose by cells (i.e., it is counter regulatory to insulin).
- K+ and Na+ excretion are decreased, while Ca2+ absorption from the intestine is increased.
- It promotes erythropoiesis [7].

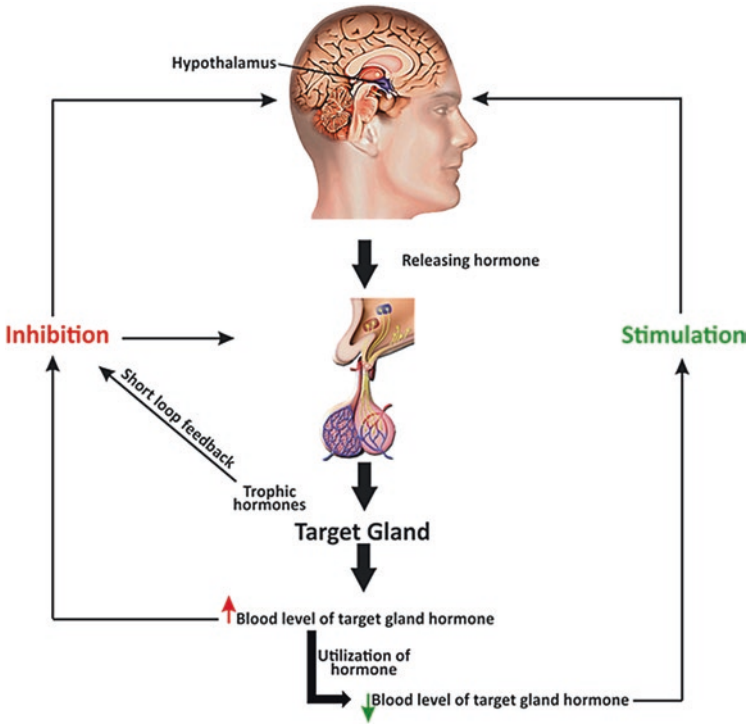

Fig. 1.3 Negative feedback regulation of secretion of hormones by the anterior lobe of the pituitary gland

Prolactin

Prolactin stimulates the secretion of milk immediately after delivery by inducing direct effect on the breast. Prolactin initiates and maintains lactation along with estrogen and progesterone. Hypothalamus releases dopamine into hypothalamohypophyseal portal system, thereby inhibiting its release. Release of prolactin releasing hormone from the hypothalamus can erratically enhance prolactin secretion, for example, whenever the infant sucks on breast [6].

Thyroid Stimulating Hormone (TSH)

Hypothalamus secretes the thyrotropin releasing hormone and transports it through the hypothalamohypophyseal portal system to the pituitary gland, thereby producing and releasing TSH from the anterior pituitary. The hypothalamus can also inhibit TSH secretion by releasing somatostatin, just as inhibition of growth hormone (GH) happens. Free T4 as well as free T3 in blood stream negatively respond/feedback the pituitary and hypothalamus in order to control the concentration of these circulating hormones.

Thyroid stimulating hormone (TSH) enhances entire known actions of cells located in thyroid gland and increases the making as well as release of T4 (thyroxine) and T3 (triiodothyroxine). There is increased vascularity and thyroid hypertrophy as a result of constant elevated levels of TSH [6].

Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH)

In women and men, the production of FSH as well as LH, respectively, in anterior pituitary is controlled via release of gonadotropin releasing hormone (GRH) from hypothalamus, which is transmitted to pituitary gland in hypothalamohypophyseal portal system. Feedback effects of testosterone, estrogen as well as statin (made in testes and ovaries in response to Follicle stimulating hormone stimulus) on the hypothalamus and together with anterior pituitary gland control levels of LH and FSH in blood stream.

In females, FSH is responsible for early maturation of ovarian follicles, while in men, spermatogenesis through Sertoli cells in the testes is stimulated by FSH. In females, LH is accountable for the final stage of maturation of follicles located in ovaries and hence the release of estrogen, while in men it makes Leydig cells in testes to release testosterone [6].

Adrenocorticotropic Hormone (ACTH)

ACTH is released from anterior lobe of pituitary gland, and is translocated along the hypothalamohypophyseal portal system to pituitary, once the hypothalamus secretes the corticotropin releasing hormone (CRH). Any type of stress that stimulates the hypothalamus is responsible for CRH release that leads to the release of ACTH in anterior pituitary, followed by secretion of cortisol from adrenal cortex. To stabilize plasma cortisol concentrations, there is a direct feedback mechanism of cortisol hormone on the hypothalamus and anterior pituitary gland.

Release of androgens as well as cortisol (hydrocortisone) from zona fasciculata and zona reticularis of adrenal cortex is stimulated by ACTH. Adrenocorticotropic hormone also has influence on zona glomerulosa cells, allowing them to make aldosterone in order to respond to decreased total sodium concentration, elevated potassium levels or higher amount of angiotensin, or in the body [6].

Posterior Pituitary Gland's Hormones

Antidiuretic Hormone (ADH)

Supraoptic nucleus of hypothalamus is mainly responsible for production of ADH. The secretion of ADH is caused by elevated plasma osmotic pressure, pain, reduced extracellular fluid volume (EFV), in addition to other stress situations, and also includes certain drugs like barbiturates and morphine. Alcohol inhibits the

secretion of ADH. ADH promotes kidney retention of water by enhancing the permeation of collecting ducts to water and following the absorption from the tubular fluid.

Oxytocin

Paraventricular nuclei is primarily involved in production of oxytocin hormone. During labor, oxytocin secretion is increased. As the fetus travel through the birth canal it stimulates the afferent nerves which is transmitted to the hypothalamus, causing oxytocin release ultimately promoting labor. When baby sucks, touch receptors located at nipple of breast communicate signals to hypothalamus that leads to secretion of oxytocin to excrete milk.

Oxytocin is mainly produced in the paraventricular nucleus. The secretion of oxytocin is enhanced during childbirth. After the fetus descends along the birth canal, it transmits impulses to the afferent nerves of the hypothalamus, causing the release of oxytocin, which increases the labor force. During breastfeeding, the tactile receptors in the breast nipple transmit a signal that terminates in hypothalamus, triggering the oxytocin secretion which is ultimately responsible for excretion of milk [6]. In a nutshell, oxytocin causes uterine contraction and stimulates lactating mammary epithelial cells to contract, causing milk to eject from the alveoli, into the mammary duct, and then from the nipple.

Thyroid Gland

Thyroid gland consists of two lobes; each is located laterally to the trachea and it is situated on neck below throat. It is said to be body's largest gland, possessing an efficient mechanism of active transport that involves absorption of iodide ions circulating in blood.

T3 and T4

The thyroid gland is accountable for the secretion of iodothyronines, three of which. The main secretory product is inactive thyroxine or T4, which is a pro-hormone of triiodothyronine or T3. T4 is converted to T3 by the periphery of type 1 deiodinase in high blood flow tissues such as liver and kidney. In the brain, type 2 deiodinase produced by glial cells converts T4 to active T3. The third iodothyronines is called reverse T3 or rT3. rT3 is inactive and is formed by type 3 deiodinase activity on T4 [8].

These iodothyronines consist of iodine and thyroglobulin. Thyroglobulin is formed from amino acids in the form of thyroid cells themselves to the apex.

Thyroglobulin is then secreted into the follicular cavity where it binds with iodide by the enzyme action to form iodinated thyroglobulin. Then, the endosome containing the iodinated thyroglobulin is fused with the lysosome to thereby enzymatically release thyroglobulin from the obtained thyroid hormone. The thyroid hormone is then released from the cells, and the remaining thyroglobulin is deiodinated and recycled [9–11].

T3 is accountable for many organs and tissues that affect the human body. In short, this can be a function of increasing protein synthesis as well as metabolic rate. T4 deficiency significantly decreases the ability of GH in order to stimulate RNA formation as well as amino acids uptake. In addition, it is important for normal organ growth, mainly in closely related regions of the central nervous system [12, 13].

Calcitonin

Parafollicular cells or C cells are accountable for the formation and secretion of calcitonin (thyrocalcitonin). Calcitonin, in contrast to parathyroid hormone, lowers blood calcium levels and maintains calcium homeostasis [14]. Calcitonin (or thyrocalcitonin) lowers the calcium blood level and majorly this calcium is deposited in bones [15].

Control System for Thyroid Hormone Secretion

Two factors are involved in thyroid hormone secretion. First is the automatic regulation of the thyroid, which can be adjusted according to the range of dietary iodide. Second one is the production of thyroid stimulating hormone from anterior lobe of pituitary gland. Additional compounds might play a role in its regulation, e.g., prostaglandins, growth factors, and neurotransmitters but their physiological significance remains to be proven. The amount of iodide is examined by its effect on thyroid hormone levels circulating in blood and the thyroid itself, thereby reducing response of thyroid cells to thyroid stimulating hormone. Increased amounts of iodine involve in inhibiting the secretion of hormones that bind to thyroglobulin, thereby reducing angiogenesis in the glands. Therefore, patients with hyperthyroidism have taken iodine before surgery [6].

Thyroid hormones (T3 and T4) work in a synergistic manner in order to maintain negative feedback mechanism of their regulation. Elevated levels of T3 as well as T4 stimulate the hypothalamus and anterior lobe of pituitary gland to shut down the secretion of TRH and TSH, respectively. On contrary, decreased levels of T3 and T4 cause the TRH and TSH genes to turn on to enhance their yield, consequently the levels of T3 and T4 are increased [16].

Parathyroid Gland

There are four parathyroid glands which are trivial, subtle clumps that project from the surface of the thyroid gland. They are of butterfly shape and are situated inside of neck, more precisely on either side of trachea. Parathyroid glands majorly play a role in controlling amount of phosphorus as well as calcium in body [17, 18].

Parathyroid glands are also involved in release of parathyroid hormones that are responsible for removal of calcium from bones into extracellular fluid by inhibiting the synthesis of osteoblasts (particular cells responsible for bone formation) and the stimulation of osteoclasts(specialized cells responsible for the removal of the bone) [19].

There are two principal cells that constitute the parathyroid tissue which are chief cells (secrete parathyroid hormone) as well as oxyphil. Morphologically parathyroid glands are largely dissimilar to thyroid gland. The main parathyroid hormone releasing cells are organized in a compact nest surrounding the small blood vessels. It is completely different from the thyroid hormone releasing cells, which are organized in spheres referred to as thyroid follicles [20, 21].

Parathyroid Hormone (PTH)

Four parathyroid glands directly release parathyroid hormone (PTH) into the blood that reaches to its targeted areas, usually located at distance. Then binding takes place between PTH and receptors present superficially or inside relevant cells. Primary target cells of PTH are present in the bone, gastrointestinal systems, and kidney. Calcitonin counteracts the production of calcium by PTH [22].

PTH opposes the action of thyrocalcitonin by eliminating calcium from the calcium storage site in the bone into the blood. In addition, PTH stimulates small intestine as well as kidneys to reabsorb extra calcium and transport it to the bloodstream. Calcium is essential for the body's metabolism, blood clotting, and skeletal muscle's contraction. Lack of PTH can cause muscle weakness and tetany due deficiency of available calcium in the blood [23, 24]. Calcium-phosphate balance between blood as well as other tissues is controlled by parathormone or PTH. Level of calcium in extracellular fluid bathing these glandular cells directly regulates secretion of this hormone (Fig. 1.4). Parathormone has the following functions:

1. It rises the absorption of calcium in GIT and transfers calcium from the intestinal lumen into the bloodstream by stimulating the active transport system.
2. It rises translocation of phosphate as well as calcium from bones to extracellular fluid by activating osteoclasts that involve in destruction of bone structure and hence rising calcium and phosphate levels in blood. As a result, the amount of calcium confined in the bone can be excavated.
3. It causes renal tubules to reabsorb more calcium thus reducing urinary elimination of calcium.

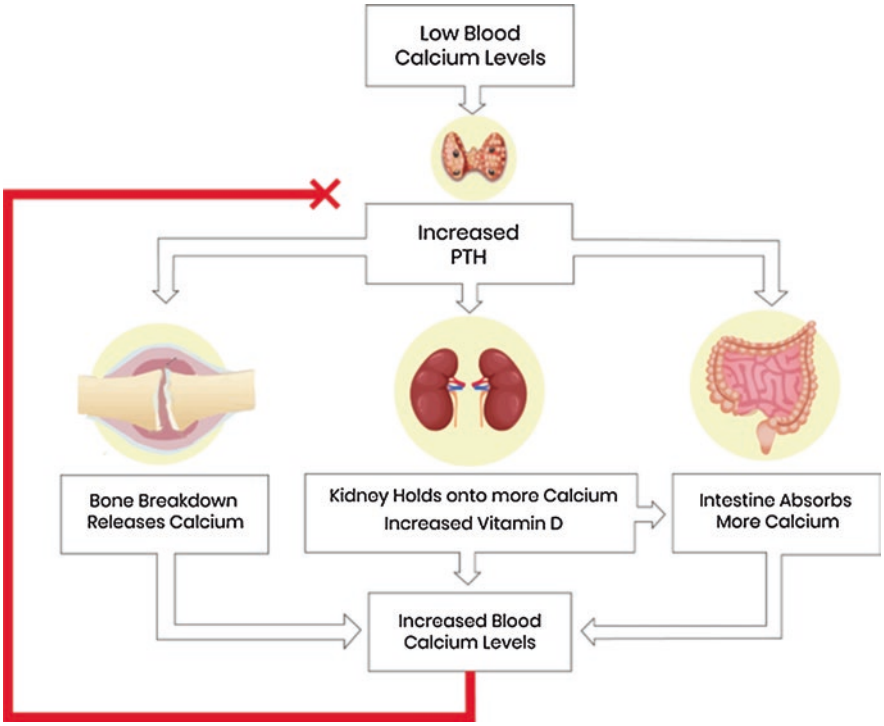

Fig. 1.4 PTH secretion regulation by the blood calcium levels

4. It decreases the phosphate's reabsorption by the renal tubules and hence prevents the kidney stones formation.
5. It increases the renal synthesis of 1,25-dihydroxycholecalciferol [1].

If the parathyroid gland is accidentally removed during thyroid surgery, the concentration of phosphate in the blood will rise. As more calcium is excreted by the kidneys and intestines and more incorporated into the bone, the concentration of calcium will also decrease. This can cause serious interference, especially innerves and muscles, which can use calcium ions to function properly. Tumors in the parathyroid glands may cause excessive activity of the parathyroid glands, resulting in weakened bones. This situation makes them more susceptible to rupture/break due to excessive calcium excretion from the bones [25, 26].

Adrenal Gland

The adrenal gland is a complex, multi-functional organ whose secretions are necessary to sustain life. Adrenal failure leads to disorders of electrolyte and carbohydrate metabolism, leading to circulatory failure, hypoglycemic coma, and death.

Each adrenal gland is located above the kidney and comprises two endocrine organs. Medial medulla of the adrenal gland is mainly involved, in response to nerve impulses, in the secretion of catecholamine adrenaline (epinephrine), noradrenaline (norepinephrine), and dopamine, which are transmitted through the preganglionic sympathetic nerve. Outer part of cortex releases glucocorticoids, sex hormones, steroid hormones, and mineralocorticoids. Two different embryological origins are involved in adrenal cortex and adrenal medulla. Chromaffin ectodermal cells of neural crest are responsible for derivation of medulla oblongata, that cleave from sympathatic ganglion cells, while coelomic mesothelium is in derivation of adrenal cortex. Blood vessels of adrenal gland are much strong, and arterial blood comes from branches of the phrenic arteries and aorta as well as from kidneys. The medulla takes blood from cortex bearing enough corticosteroids that controls formation of enzymes responsible for conversion of noradrenaline to adrenaline. Venous blood drains mainly into renal vein or inferior vena cava through the large adrenal vein [1].

Adrenal Medulla

Adrenal medulla is an altered sympathetic ganglion consisting of dense innervated granules containing cells, accounting for approximately 30% of the adrenal structure. About ten percent of the cells are responsible for noradrenaline secretion, while 90% are chiefly epinephrine secreting cells. It is not clear which kind of cells involved in dopamine release. A little portion of chromaffin cells are also positioned outer side of the medulla, generally next to the sympathetic ganglion chain [6].

Catecholamines

Epinephrine, norepinephrine, and dopamine are packed in membrane bound granules; their emission is triggered by the secretion of acetylcholine from sympathetic nerve fibers which propagate into splanchnic nerves. The half-life of catecholamines in plasma is very short, ≥2 min. Removal from bloodstream includes absorption of both neuronal as well as non-neuronal tissues in which their degradation or recycling by catechol-O-methyltransferase or monoamine oxidase occurs. Approximately fifty percent of the released catecholamines are present in the urine as free or bound meta-adrenalines and normetadrenalines, while approximately 35% of the vanillylmandelic acid (VMA) form appears. Catecholamine's release is lower in the basal state but it is further reduced during nap. Sympathetic activity controlled by the hypothalamus is involved in their secretion and happens in order to respond to excitement, hypoglycemia, hypovolemia, anxiety, and pain. You get diffuse medullary discharges through an emergency stimulus, making patients to combat or evasive reactions. The effects of noradrenaline and adrenaline are various and complicated, depending on their bounding with alpha (α1, α2) and beta (β1, β2) adrenergic receptors, whereas dopamine also has effect on particular dopaminergic receptors. They mimic action of noradrenergic nerve discharge, stimulate the

nervous system, as well as induce metabolic actions, including glycogen breakdown in skeletal muscle and liver, increased plasma lactate, mobilization of free fatty acids, and increased metabolic rate. Due to extensive vasoconstriction, noradrenaline causes a significant increase in peripheral vascular resistance, while adrenaline causes vasoconstriction of visceral organs and skin but vasodilation of the skeletal muscle that ultimately decreases total peripheral resistance (TPR). Thus, collective action of both results in increased myocardial rate, but the intake of noradrenaline is responsible for reflex bradycardia that occurs as a result of a significant increase in mean arterial and peripheral resistance. Even though adrenaline often causes anxiety and fear in humans, they increase alertness [6].

Adrenal Cortex

Adrenal cortex is accountable for the release of mineralocorticoids, androgens (sex hormones), and glucocorticoids. Glucocorticoids have effect on metabolism of carbohydrates, fats, and proteins and are essential in facilitating responses to stress as well as fasting. Mineralocorticoids are important in order to keep balance for sodium and thus extracellular fluid balance. Compared with the pituitary hormones FSH and LH, androgen has little effect on reproductive function. Adrenal cortex is histologically divided into three distinct layers. The extreme layer contains zona glomerulosa, central layer (major layer) consists of zona fasciculate cells, and the innermost layer comprised of zona reticularis. Corticosterone is secreted in all three regions, whereas biosynthesis of aldosterone occurs in zona glomerulosa. The enzymatic mechanisms that form cortisol (hydrocortisone) and androgens are mainly present in two internal regions.

Glucocorticoids

The adrenocorticotropic hormone (ACTH) secreted by the anterior lobe of pituitary gland regulates the release of glucocorticoids. It is regulated via hypothalamic discharge of corticotropin releasing hormone (CRH) into hypophyseal portal system. Cortisol secretion induces a negative feedback influence on the anterior lobe of pituitary gland as well as hypothalamus. Cortisol amount in plasma was in diurnal mode and maximum amount is observed just before awaking in the morning (Fig. 1.5). The circulating corticosteroids primarily bind to plasma proteins, i.e., corticosteroid binding globulin (transcortin) as well as albumin. Hormones are deactivated mainly in the liver by binding with sulfate or glucuronic acid and are excreted into the urine. Glucocorticoids play a vital role in controlling metabolism of carbohydrates, proteins, and fats. They stimulate the storage of liver glycogen. During fasting, they trigger formation of glucose in the liver in order to supply glucose for brain metabolism. They have an antagonistic effect on insulin, leading to an increase in blood sugar. Glucocorticoids enhance the vasoconstriction of catecholamines and reduce the permeation of vascular endothelium that is crucial for

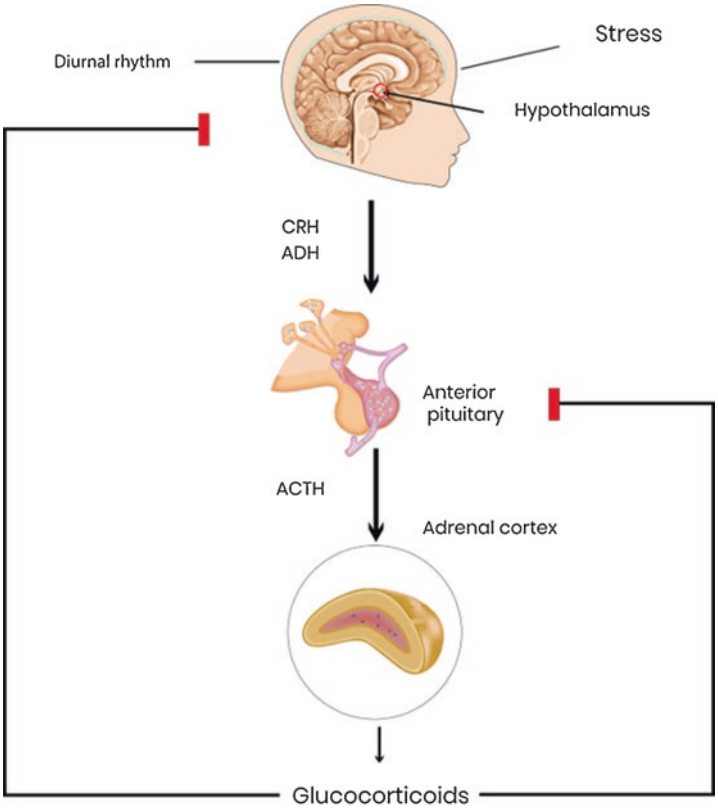

Fig. 1.5 The regulation of glucocorticoids

maintaining normal function of vascular system. Cortisol secretion rises during anxiety and in patients having adrenal insufficiency, the deficiency of this response leads to hypotension that ultimately results in death. Glucocorticoids have certain mineralocorticoid action as well. It has been found that they bear anti-inflammatory activities and can stamp down responses of immune system [6].

Mineralocorticoids

Aldosterone and other steroidal mineralocorticoid (deoxycorticosterone, corticosterone) increase sodium reabsorption, acting primarily on distal tubules of kidneys, leaving sodium in the extracellular fluid. Actually, sodium is replaced with potassium as well as hydrogen, eventually results in potassium excretion in urine and acidic urine. In the case of adrenal inefficiency, potassium is retained, while sodium is excreted in the urine that results in elevated level of potassium in plasma and hypovolemia, leading to hypotension and circulatory insufficiency.

Renin-angiotensin mechanism plays a main part in maintaining electrolyte balance and blood volume. The core factors controlling aldosterone release include renin-angiotensin system, the adrenocorticotropic hormone (ACTH) produced by pituitary gland, and increase in plasma potassium or decrease in plasma sodium, thereby directly stimulating the adrenal cortex. Aldosterone is just one of the numerous elements that affect sodium excretion. While other main elements comprise atrial natriuretic peptide, glomerular filtration rate, and alterations in renal tubular reabsorption of sodium (independent of aldosterone). The main function of the aldosterone secretion mechanism may be to maintain the intravascular volume, although several other mechanisms are involved [6].

Pineal Gland

Pineal gland (epiphysis or pineal body) is a tiny ductless gland in brain. This is situated close to the midpoint of brain between hemispheres and is hidden in a groove connected by two circular thalamus bodies. The pineal gland appears to be a red-gray body having a size of a pea about 8 mm in human beings. It is positioned behind and below the stria medullaris, outside of the superior colliculus, and amid of laterally positioned thalamic bodies. This is part of upper epitheliums. As pineal gland is a midline structure, so this can generally observe in calcified skull X-rays. Melatonin is the chief hormonal secretion of pineal gland. The discharge is at its peak level between 0 and 5 years old and at night time [27].

The Gonads

The gonads comprise testes and ovaries that have two main roles: (a) production of germ cells (sperm by testes and eggs in ovaries) (b) they synthesize steroidal sex hormones. These hormones are involved in development and functioning of male and female sex organs as well as secondary features (e.g., male facial hair) and pregnancy, delivery, and breastfeeding. There are three categories of sex hormones, each regulating a discrete function. Sex hormones also play many important roles in the body in addition to reproductive function. For instance, they have effect on metabolism of lipid and carbohydrates, growth and development of bones and cardiovascular system [28].

Estrogens

Estrogen is mainly estradiol that is formed principally within ovaries except for a small amount of estrone and estriol. Other synthesis sites for estrogen exist in corpus luteum, adrenal gland, and placenta. In postmenopausal women as well as in

men, most of the estrogen circulating in the blood circulation comes from alteration of adrenal, ovarian, and testes androgens. Transformation happens in surrounding tissues, mainly adipose tissue and skin. Principally estrogens are responsible for keeping harmonization between the normal development and function of female breasts and genitals. Estrogen promotes growth of vagina, uterus, and breasts during puberty. They also regulate fat distribution and deposition patterns throughout body that lead to typical female body types; control puberty climax and stop growth after adulthood; and control development of secondary sexual features [29]. In young females, the main roles of estrogen comprise regulating the menstrual cycle, promoting hormone regulation of pregnancy and breastfeeding, and maintaining female sexual desire. The production of estrogen in the ovaries stops during menopause. Reduced levels of estrogen cause symptoms such as sweating, hot flashes, palpitations, elevated irritability, depression, anxiety, and bone fragility (i.e., osteoporosis). Administration of estrogen (i.e., hormone replacement therapy; HRT) in postmenopausal women can lessen these signs and decrease the danger of coronary heart disease as well as osteoporosis. However, hormone replacement therapy may enhance the chances of developing particular kinds of cancer such as uterine (endometrial) cancer and breast cancer [30].

Progestogens

The ovaries produce progesterone at some stage of the menstrual cycle and in most of the pregnant placenta. Progesterone causes alterations in the endometrium to prepare for pregnancy, and along with estrogen stimulates mammary glands for lactation. The main progestogen is progesterone [31].

Androgen

Testosterone is main androgenic steroid that is mainly discharged from the testes, but it is released from adrenal glands in both male and female as well and in small amounts from ovaries. Key function of testosterone is to trigger growth and development of reproductive tract in men. Additionally, testosterone has a strong effect on protein anabolic activity. Thus, it encourages formation of protein resulting in augmented muscles mass. Certain roles of testosterone differ at diverse phases of development, as follows:

- During fetal stage, testosterone principally makes sure the development of internal as well as external male genitalia.
- At puberty, this hormone triggers growth of sexual organs in men and is responsible for additional developmental features of males like puberty spurts and eventually cessation in adult height development; deeper voice; axillary, pubic, body, and facial hair growth; and increased muscle and strength.

- During adulthood in men, this is predominantly responsible for sustaining masculinity, sexual ability, libido and controlling spermatogenesis. Little decrease in testosterone amount with age occurs, but this decline is not as much as the decreased estrogen levels in menopausal females [29].

Pancreas

Pancreas is an important viscera of digestive system as well as circulatory system because it assists in maintaining our blood glucose levels. It is of pear shape having a length of 6 inches, situated at mid and posterior to abdomen. This is attached to duodenum and is located behind stomach. Pancreas is considered to be a part of the digestive tract as it secretes enzymes responsible for digestion. These digestive enzymes help to breakdown food in to essential entities that are absorbed via intestine and ultimately used by the body. The secretion of these digestive enzymes into small intestine executes exocrine role of the pancreas, where particular entities delivered directly to another organ. The pancreas is an endocrine as well as exocrine gland [28].

It also has a significant endocrine role. A small group of cells in the entire organ called islet cells produce insulin and glucagon (hormones that are important to control glucose amount in blood). Insulin and glucagon are released directly into the blood, thus affecting organs of entire body. Pancreas is the only viscera that forms ample amount of glucagon and insulin. Insulin is responsible for lowering blood glucose levels by permitting flow of glucose into the cells. Glucagon increases blood glucose levels as a result of releasing glucose from its storage site into the circulation. Insulin and glucagon have antagonistic effect on blood glucose level in order to keep blood glucose levels stable. A normal functioning of pancreas is responsible for good health by maintaining malnutrition and normal blood glucose concentration. Hormones of pancreas are helpful in gastrointestinal tract in order to breakdown the food particles to the simplest elements, otherwise the absorption of nutrients cannot take place, e.g., macromolecules like carbohydrates must be catabolized into simplest glucose molecules, fat into fatty acids, and protein into simple amino acid. Pancreatic enzymes are significant in all of these reactions. So, these elements can be transported easily into the intestine where they are further transformed and taken away to different tissues of body as fuel sources as well as building materials. Likewise, without balance between insulin and glucagon action, the body will not be able to maintain normal blood sugar levels [29].

Insulin

The pancreas consists of endocrine and exocrine cells. The islets of Langerhans (groups of endocrine cells) release two types of hormones. Alpha cells release glucagon and beta cells secrete insulin. The amount of sugar in the blood depends on the opposite effect of these two hormones. Insulin causes hypoglycemia. So, major

portion of blood glucose enters liver and skeletal muscle cells and here monosaccharaides are converted into polysaccharide glycogen. Therefore, insulin stimulates glycogen production (glycogenesis) and also stimulates its decomposition to glucose and ultimately its release into the bloodstream. Insulin deficiency leads to diabetes mellitus, especially type I (juvenile diabetes). In type II diabetes, the pancreas yields enough insulin, but the target areas of body do not respond to it [1].

Insulin is the hormone that produces actions directly or indirectly on most parts of the body, except for the brain. Significant function of insulin is to stimulate many tissues, especially the liver, fat, and muscles to absorb glucose. Uptake of glucose by cells reduces glucose in blood and enhances the availability of glucose for cellular responses where glucose is involved. Therefore, glucose uptake can exacerbate glucose oxidation, and glycogen and fat synthesis. Insulin does not alter the brain's absorption of glucose and does not have any effect on active transport of glucose in the gastrointestinal epithelial cells and renal tubules. As mentioned above, insulin triggers glycogenesis. Furthermore, it also escalates the enzymatic activity that catalyzes the rate-limiting step in glycogenesis. It also augments the level of triglycerides by inhibiting the breakdown of triglycerides and by stimulating the production of triglycerides by synthesis of fatty acids and glycerophosphates. Insulin can also enhance the net synthesis of proteins, thereby stimulating the active membrane transport of amino acids, especially into muscles. It also affects other hepatic enzymes, but the exact mechanism by which insulin induces these modifications is not well comprehended [3].

Glucagon

These alpha cells of islets of Langerhans secrete glucagon. Glucagon has the following functions:

- It increases the glucose synthesis from the liver by pyruvate, lactate, glycerol, and amino acids by gluconeogenesis, hence glucose level in the plasma is also increased.
- It rises the decomposition of triglycerides in adipose tissues, and ultimately there is increased level of glycerol and fatty acids in the plasma.
- Like beta cells, glucagon secreting alpha cells react to glucose level fluctuations in the hepatic blood without the involvement of other nerves or hormones.

Glucagon acts in an antagonistic manner to insulin:

1. Glucagon raises plasma glucose in contrary to insulin which increases its uptake and hence lowers glucose level in the plasma.
2. Glucagon raises the concentrations of fatty acid, while insulin transforms fatty acids and glycerol to triglycerides, hence inhibits the triglycerides' decomposition.

The pancreatic alpha and beta cells constitute a push-pull system for controlling plasma glucose level [4]. A brief summary of different endocrine hormones, their function, and the diseases related to these hormones is mentioned in Table 1.2 [1, 28, 32–35].

Table 1.2 A brief description of endocrine hormones, their function, and related disorders

Endocrine gland	Hormone	Specific function	Endocrine disorders
Anterior pituitary gland	Growth hormone (GH)	Stimulates the growth and development of the body	Hypersecretion of GH during childhood causes gigantism, during adulthood causes acromegaly Hyposecretion of GH during childhood causes dwarfism
	Prolactin	Stimulates lactation (milk production right after delivery)	Hyperprolactinemia or Galactorrhea
	Thyroid stimulating hormone (TSH)	Stimulates the release of thyroid hormones (T3 and T4) and increases all known activities of thyroid gland	
	Follicle stimulating hormone (FSH)	Stimulates spermatogenesis through Sertoli cells in the testes (in men) Stimulates early maturation of ovarian follicles (in women)	Ovarian hyperstimulation syndrome Hypergonadotropic—hypogonadism (Klinefelter's syndrome, Turner syndrome) Hypogonadotropic—hypogonadism (Kallmann's syndrome)
	Luteinizing hormone (LH)	Stimulates testosterone secretion from Leydig cell in the testes (in male) Responsible for final maturation of ovarian follicles and the secretion of estrogen therein (in female)	
	Adrenocorticotropic hormone (ACTH)	Stimulates the secretion of cortisol (hydrocortisone) and androgens	
Posterior pituitary gland	Antidiuretic hormone (ADH)	Maintains the water and electrolyte balance in the body	Diabetes insipidus
	Oxytocin	Stimulates uterine contraction during labor and promotes milk ejection during breastfeeding milk ejection in nursing women	Deficiency may cause Autism

(continued)

Table 1.2 (continued)

Endocrine gland	Hormone	Specific function	Endocrine disorders
Hypothalamus	Growth hormone releasing hormone (GHRH)	Stimulates the secretion of GH from the anterior pituitary gland	
	Corticotrophin releasing hormone (CRH)	Stimulates the secretion of ACTH from posterior pituitary	
	Gonadotropin releasing hormone (GnRH)	Stimulates the secretion of FSH and LH from the anterior pituitary	
	Thyrotropin releasing hormone (TRH)	Stimulates the secretion of TSH from anterior pituitary	
	Somatostatin	Inhibits GH secretion from anterior pituitary	
	Dopamine	Inhibits prolactin secretion from anterior pituitary	
Thyroid gland	Thyroid hormones T3 (triiodothyronine) and T4 (thyroxin)	Maintenance of metabolic processes and plays a vital role in protein synthesis, normal growth, and organ development	Hyperthyroidism: Graves' disease Hyposecretion: Cretinism (during growing years)
	Calcitonin	Lowers blood calcium levels and maintains calcium homeostasis	Myxedema (in adults) Hyposecretion: Ricketts in children
Parathyroid gland	Parathyroid hormone (PTH)	Regulates the calcium-phosphate balance between blood and other tissues by increasing blood calcium levels	Hyperparathyroidism Hypoparathyroidism
Adrenal cortex	Cortisol (glucocorticoid)	Control the metabolism of fat, carbohydrates, and proteins. Cortisol release rises during stress and adrenal insufficiency thus protect from hypotension and death	Hypersecretion: Cushing's syndrome Hyposecretion: Addison's disease
	Aldosterone (mineralocorticoid)	Regulate the water and electrolyte balance in the body	Primary hyperaldosteronism (Conn's syndrome)

(continued)

Table 1.2 (continued)

Endocrine gland	Hormone	Specific function	Endocrine disorders
Adrenal medulla	Epinephrine and norepinephrine (catecholamine's)	Have effect on the same organs as of sympathetic nervous system, i.e., smooth muscles, glands, and heart and prolong or enhance the effects produced by sympathetic nervous system	
Ovaries	Estrogen	During puberty regulates the development of female reproductive organs, while in adult women regulates the menstrual cycle, promotes hormone regulation of pregnancy and lactation, and maintaining female sexual desire	Polycystic ovarian syndrome (PCOS)
	Progesterone	Causes alterations in the endometrium to prepare for pregnancy, and together with estrogen stimulates breast development in the mammary glands to prepare for lactation	Adrenogenital syndrome Masculinizing effect
Testes	Testosterone	Stimulates the growth and development of the male reproductive tract, sperm production and also possesses strong protein anabolic activity (promoting protein production, resulting in increased muscle mass)	Hypogonadism (infertility) Erectile dysfunction
pancreas	Insulin	Lowers concentration of glucose in blood by regulating carbohydrate metabolism	Diabetic mellitus Diabetic ketoacidosis Hypoglycemia
	Glucagon	Increases concentration of glucose in blood by regulating carbohydrate metabolism	Glycogen storage disease (GSD)

(continued)

Table 1.2 (continued)

Endocrine gland	Hormone	Specific function	Endocrine disorders
Pineal gland	Melatonin	Regulates menstrual cycle in females and inhibits onset of puberty in males	Peptic ulcer Psychotic depression
Thymus	Thymosin and related hormones	Stimulates the development of lymphatic organs Induces maturation and development of WBC's particularly T-lymphocytes	Myasthenia gravis (MG) Pure red cell aplasia (PRCA) Hypogammaglobulinemia

Metabolic Disorders

Thyroid Gland Related

Hyperthyroidism

Hyperthyroidism is thyroid gland's hyperactivity which is known as thyrotoxicosis (hyper metabolic state). Thyroid storm is a rare but life-threating condition which occurs in just 1–2% of hyperthyroidism patients. Another most usual type of hypothyroidism is Graves' disease. It is an autoimmune disease in which thyroid hormone's secretion is enhanced by the antibodies mimicking the effects of TSH. This disease can occur in any age but most commonly found in middle-aged women and can also affect men. There are some other causes of hyperthyroidism, i.e., acute poisoning triggered by thyroid hormones (exogenous), high iodine-loaded drugs (such as amiodarone or iodine iodinated IV agents), resulting in abrupt excessive thyroid hormone's secretion in susceptible individuals. As a result of thyroid gland's autoimmune destruction, temporary hyperthyroidism may occur, followed by chronic hypothyroidism. Thyroid storm occurs when the body is under stress due to adverse reaction of a drug, diabetic emergency, or some other serious challenges. If the patient is suffering from cardiac decompensation after taking amiodarone, an iodine-rich antiarrhythmic drug, thyroid storm should be suspected [36].

Signs and Symptoms

Typical clinical manifestations of patients with hyperthyroidism include anxiety, heart palpitations, agitation, impatience, and weight loss (up to 40 pounds/few months). Excessive sweating and intolerance of heat caused by this metabolic abnormality is a common symptom. Signs and symptoms of thyrotoxicosis will be revealed after a thorough physical examination, which specifically include a

common characteristic of this disease, i.e., exophthalmos. Patients usually experience weight loss, heat intolerance, tachycardia, palpitations, proptosis, and diffuse enlargement of thyroid gland. Another rare form of thyrotoxicosis is Apathetic thyrotoxicosis which only occurs in the elderly. There are no typical hyperthyroidism's symptoms in this condition. The patient is drowsy, experiences anesthetic effect, progresses to goiter, and also experiences weight loss [37].

Hypothyroidism

Hypothyroidism is caused by a decrease in overall metabolism due to insufficient thyroid hormone levels in the body. Hypothyroidism falls into two broad categories [38]:

Primary Hypothyroidism Primary hypothyroidism occurs due to insufficient hormones as a result of less hormonal secretion or destruction of thyroid tissue responsible for secretion.

Hashimoto's Thyroiditis It is an autoimmune disorder and main cause of primary hypothyroidism in the USA**.** In this condition, thyroid cells and related enzymes are being attacked by the body's own immune system leading to thyroid cells destruction and lessen the ability of gland to produce thyroid hormones [39].

Secondary Hypothyroidism It occurs as a result of hypothalamic disease or pituitary gland's pathology leading to insufficient release of thyroid and secondary thyroid stimulating hormone, resulting in inadequate thyroid hormone level [40].

Signs and Symptoms

Hypothyroidism imparts damaging effects on various body systems, i.e., metabolism, cardiovascular, and nervous system. The patient's skin in this condition is cool, yellow, and dry. Patients often have thinning eyebrows, rough skin as well as hair, significant intolerance to cold, and alterations in the nervous system, such as ataxia, alterations in mental status, and prolonged relaxation of deep tendon reflexes. A life-threatening condition called myxedema coma may occur as a result of chronic and extreme hypothyroidism, which is characterized by hypoglycemia, hypotension, bradycardia, and low serum sodium (hyponatremia) [2].

Iodine Deficiency

Iodine deficiency is the most common cause of hypothyroidism in developing countries. Since iodine is crucial for the production of thyroid hormones, the disease establishes itself as congenital hypothyroidism in infancy. Patients will experience

a variety of physical malformations, delayed growth, and brain dysplasia. Eventually, this situation can be reversed by appropriate supplementation of iodine [41]. Other diseases related to thyroid abnormalities include [42]:

- Subacute granulomatous thyroiditis
- Riedel fibrosing thyroiditis
- Wolff–Chaikoff effect
- Thyroid storm
- Toxic multinodular goiter

Parathyroid Gland Related Disorders

Hypoparathyroidism

Hypoparathyroidism occurs due to decreased levels of PTH in serum or resistance to PTH's effects. Other reasons may include acquired, autoimmune, or congenital diseases. This disease is marked by hypocalcemia irrespective of any cause. Acquired hypoparathyroidism is commonly caused by iatrogenic injury or accidental resection of the gland during thyroidectomy. The injury (e.g., during neck cleaning) may be temporary or permanent.

Signs and Symptoms

Signs and symptoms of acute hypoparathyroidism include tetany, paresthesia, and muscle spasms. Sometime patient may experience a seizure. All these signs and symptoms are attributable to hypocalcemia [43].

Adrenal Gland Related Disorders

Acute Adrenal Insufficiency

Acute adrenal insufficiency is the condition in which body requires more glucocorticoids and mineralocorticoids beyond the limit of adrenal gland, responsible for secreting these hormones. The main cause of this condition is the sudden withdrawal of steroidal drug therapy after being used for long period. It may also arise when such patients fail to get a dose in stress, e.g., during a disease or after major trauma or surgery. Acute dysfunction is classified into primary, secondary, or tertiary according to the endocrine gland's dysfunction. Primary adrenal insufficiency refers to adrenal dysfunction, secondary adrenal insufficiency refers to pituitary dysfunction, and tertiary renal insufficiency is associated with hypothalamic dysfunction [44].

Signs and Symptoms

Clinical manifestations of this condition include weakness, nausea, abdominal pain, vomiting, and dehydration. Some historical evidences, such as the tan skin of a patient refusing to receive sunlight, may specify chronic adrenal insufficiency. Adrenal insufficiency along with hypotension is called the adrenal crisis and institutes real life-threatening crises [45].

Chronic Adrenal Insufficiency

Adrenal insufficiency results from inability of adrenal cortex to release cortisol in an adequate amount. It can be classified as primary, secondary, or tertiary which is dependent on either cortex is damaged directly or indirectly. *Addison's disease* (primary adrenal insufficiency) is a metabolic as well as endocrine disease resulting from direct injury or failure of the adrenal cortex. This is a chronic ailment having a long-term attack. Primary adrenal insufficiency may occur whenever there is a direct damage to adrenal cortex, i.e., adrenal hemorrhage, autoimmune diseases, tuberculosis (infectious diseases), meningococcemia pathophysiology, and acquired immunodeficiency syndrome (AIDS) [46]. As mentioned earlier, the adrenal cortex secretes the corticosteroids aldosterone and cortisol. Aldosterone is responsible for maintaining a balance of serum levels of potassium and sodium. Whenever body is under any stress (such as trauma, heart ischemia, infection, or serious illness), the adrenal gland may not be able to produce adequate amount of corticosteroids to meet the body's needs, causing acute exacerbations of Addison's disease. Although in secondary adrenal insufficiency, the cortex itself remains intact, since the pituitary does not release the adrenal cortex hormone (ACTH), which normally stimulates the adrenal cortex, the pituitary does not release cortisol, hence adrenal insufficiency is one step lesser. Therefore, adrenal insufficiency is a step removal. The reason for the third-level (tertiary) adrenal insufficiency is more direct, because the pituitary cannot release ACTH because of pituitary hypothalamic disease [47]. Primary adrenal insufficiency may include hyperpigmentation due to excessive production of melanocyte stimulating hormone (MSH) which is due to the reason that both MSH and ACTH are secreted by the single precursor protein in the pituitary named pro-opiomelanocortin. MSH is responsible for stimulating melanocytes for the production of melanin. Secondary and tertiary adrenal insufficiency are associated with decreased levels of MSH so cannot be connected with hyperpigmentation of skin [46].

Signs and Symptoms

Signs and symptoms of Addison's disease are mostly associated with the endocrine and electrolyte disturbances which are characteristic of this disease. Due to excessive MSH, the patient will experience loss of appetite, weight loss, weakness, chronic fatigue, and hyperpigmentation of the skin and mucous membranes. Patients may experience electrolyte disturbances accompanying hyperkalemia,

hyponatremia, and hypotension, as well as gastrointestinal illnesses such as nausea, vomiting, abdominal pain, and diarrhea [48].

Hyperadrenalism (Cushing's Syndrome)

Hyperadrenalism also known as Cushing's syndrome occurs as a result of long-term exposure to excessive glucocorticoids especially cortisol in serum due to overproduction of the adrenal cortex. Among women, it is more common, especially between the ages of 20 and 50. Cushing's syndrome may occur due to pituitary or adrenal tumors or long-term use of corticosteroids [38].

Irrespective of the cause, excessive cortisol may lead to specific changes in various body systems. Metabolism of carbohydrates, fats, and proteins is interrupted, leading to elevated blood sugar levels. Protein synthesis is impaired, and human proteins break down, leading to muscle fiber loss and muscle weakness. The bones are weaker and more prone to fractures [43].

Signs and Symptoms

Cushing's syndrome's patients have a discrete look characterized by lunar face, obesity, and other major features. Signs and symptoms often associated with this disease include [49]:

- Full, puffy face
- Increased body and facial hair
- Thin, fragile skin
- Chronic weakness
- Diabetes mellitus (DM)
- Fatty "buffalo hump" on exterior neck
- Atrophied proximal muscles
- Central body obesity
- Amenorrhea
- Purple striae on the arms, breasts, abdomen, or buttocks
- Hypertension
- Decreased fertility or diminished sex drive

Pituitary Gland Related Disorders

Acromegaly

Acromegaly is a rare systemic disease that affects the full body [50]. It occurs when the body fails to regulate the excessive production of GH [51]. Since GH promotes the growth of muscles, internal organs, and bones and causes the secretion of

insulin-like growth factor 1 (IGF-1) [52], so, in acromegaly, there is an increased level of both hormones, i.e., GH and IGF-1 leading to tissue enlargement and metabolic alterations which ultimately causes visible malformations and increased mortality [53]. This disease usually occurs between the ages of thirty and fifty. The onset is concealed and progresses slowly, often delaying the diagnosis to the late stage of the disease [51]. GH counteracted the effects of insulin on glucose metabolism. It also regulates tissue response to insulin; consequently, increased GH may be the cause of insulin resistance. Acromegaly is associated with abnormal lipid metabolism. The study found that patients with acromegaly had higher serum triglyceride levels [54].

Hyperprolactinemia or Galactorrhea

The galactorrhea is lactation in non-breastfeeding women or in men. The galactorrhea is usually caused by a pituitary adenoma (prolactinoma) that secretes prolactin. Most of the tumors in women are microadenomas (<10 mm in diameter), but only a small fraction of them are large adenomas (>10 mm) after diagnosis. The frequency of microadenomas in men is quite lesser, which may be due to later recognition. Pituitary non-functional lesions can also increase prolactin levels by compressing the pituitary stalk, thereby reducing the action of the prolactin inhibitor dopamine.

Hyperprolactinemia and galactorrhea may also be caused by certain medications, including phenothiazine and some other antipsychotics, opioids, and certain antihypertensives (especially alpha-methyldopa). Primary hypothyroidism can cause galactorrhea and hyperprolactinemia, as elevated levels of thyroid releasing hormones increase the secretion of prolactin and TSH. Hyperprolactinemia may be associated with gonadotropin deficiency and hypogonadism, possibly by inhibiting the release of gonadotropin releasing hormone (GnRH) or acting on pituitary gonadotropins [52].

Signs and Symptoms

There is no quantitative definition of lactation abnormalities. Milk release is inappropriate for the patient, persistent or worrying. Impulsive lactation is rare than milk released in response to artificial expression. The milk is white and the fat globules can be seen when the sample is examined with a microscope. Women with galactorrhea usually have amenorrhea or oligomenorrhea. Because high prolactin levels inhibit the release of gonadotropin and follicle stimulating hormone, women with galactorrhea and amenorrhea may also have signs and symptom of estrogen deficiency, including difficulty in sexual intercourse and decreased libido. However, estrogen secretion may be normal, and signs of excessive androgen, including hirsutism, are observed in some women with hyperprolactinemia. Hyperprolactinemia may cause other menstrual cycle disorders other than amenorrhea, including fewer ovulations and luteal dysfunction. Men with prolactin secreting pituitary tumors

cause visual difficulties or headaches. About two-third of men affected by this disease experience loss of libido and erectile dysfunction [55].

Erectile Dysfunction (ED) or Impotence

Erectile dysfunction (ED) refers to an erection that is unable to obtain or maintain sexual satisfaction. Every man infrequently encounters an erection problem, which is considered normal. Erectile dysfunction (ED) occurs when a man:

- Attains erection briefly but not long enough for intercourse
- Never able to attain an erection
- Inconsistently attains effective erection

If the person has never been able to erect or maintain an erection, the ED is referred to as the primary ED. If the ED is developed by a man in late age who was previously able to erect, it is called secondary ED. Secondary ED is more common than primary ED. In the USA, approximately 50% of men between the ages of 40 and 70 are affected to some extent, and this proportion increases with age. However, ED is not considered to be a normal part of aging and can be successfully treated at any age. In order to reach an erectile state, the penis needs to have enough blood flow, the normal function of the nerves leading to and from the penis, the blood flowing out slows down, the sufficient amount of male sex hormone testosterone and enough libido (sexual desire), and therefore any of these system's disease can cause erectile dysfunction (ED) [56].

The most common particular causes are:

- Diabetes mellitus
- Hardening of the arteries (atherosclerosis) that interrupts the blood flow to the penis
- Certain drugs, such as drugs for the treatment of hypertension or prostatic hypertrophy, and drugs that act on the central nervous system, such as drugs for the treatment of depression
- Complications of prostate surgery

Signs and Symptoms

In men with ED, certain signs and symptoms are of concern. They include the following:

- There is no erection when you wake up at night or in the morning.
- Painful cramps in the leg muscles occur during physical exercise, but can be relieved immediately after a break (claudication).
- A sense of numbness between and around the buttocks and genital area (called the saddle area).

Central Diabetes Insipidus

Diabetes insipidus occurs as a result of vasopressin's (antidiuretic hormone) deficiency. This antidiuretic hormone's (ADH) deficiency is produced by hypothalamic-pituitary disease (central diabetes insipidus) or renal resistance to vasopressin (nephrotic diabetes insipidus). As a result polydipsia and polyuria occur. Vasopressin promotes water preservation effects in the kidney primarily by enhancing the permeability of the distal tubular epithelium to water. Vasopressin also causes vasoconstriction at high concentrations. Like aldosterone, vasopressin also plays an important role in preserving humoral homeostasis as well as cellular and vascular hydration. The main stimuli of vasopressin secretion are an increase in osmotic pressure of water in the body (perceived by the osmoreceptors of the hypothalamus) and volumetric consumption (perceived by vascular baroreceptors). Vasopressin is synthesized in the hypothalamus, while the main storage site of it is posterior pituitary. The freshly synthesized hormone can be secreted into the circulation if hypothalamic nucleus and neurohypophysis regions are intact. To avoid central diabetes insipidus, at least 10% of neurosecretory neurons should remain intact. Therefore, central diabetes insipidus pathology always encompasses the paraventricular and supraoptic nucleus of the key part of the hypothalamus or pituitary stalk. Central diabetes insipidus may be partial (insufficient amounts of vasopressin) or complete (absence of vasopressin). It can also be primary (an obvious reduction in the hypothalamic nuclei of the neurohypophyseal system) or secondary (acquired).

Primary Central Diabetes Insipidus

The genetic abnormality of the vasopressin gene on chromosome 20 is an autosomal dominant form of primary central diabetes insipidus, but many cases are idiopathic.

Secondary Central Diabetes Insipidus

Central diabetes insipidus may also be secondary (acquired), caused by a variety of lesions, i.e., pituitary resection, suprasellar or intrasellar tumor (primary or metastatic) craniocerebral injury (especially basal skull fracture), sexuality, Langerhans cell histiocytosis, granuloma (sarcoidosis or tuberculosis), lymphocytic pituitary inflammation, infection (encephalitis, meningitis), and vascular disease (aneurysm, thrombosis).

Signs and Symptoms

The onset of central diabetes insipidus may be occult or sudden, which may occur at any age. Symptoms of primary central diabetes insipidus are polyuria and polydipsia. In secondary central diabetes insipidus, there are also signs and symptoms of

related lesions. In this condition patient may ingest large amounts of fluid and excrete large amounts (3–30 L/day) of very dilute urine. Nocturia almost always occurs. If the urine lost is not continuously replenished, dehydration and insufficient blood volume may occur rapidly [57].

Hypopituitarism

Hypopituitarism is a rare disease which occurs as a result of decrease secretion of one or more pituitary hormones. It can be caused by a variety of factors, including inadequate supply of blood to the pituitary gland, certain inflammatory diseases, or pituitary tumors. Pituitary gland is mostly affected by:

- Inadequate supply of blood to the pituitary gland (due to anemia, blood clots, severe bleeding, or other conditions)
- Pituitary tumors
- Tumors of the hypothalamus
- Causes affecting primarily the hypothalamus, which then affects the pituitary
- Deficiencies of hypothalamic hormones
- Inflammatory disorders (such as sarcoidosis)
- Infections
- Autoimmune disorders
- Inflammation of the pituitary due to anticancer monoclonal antibody drugs (ipilimumab or related drugs)
- Inflammatory disorders
- Head injuries
- Surgical removal of pituitary tissue
- Irradiation (as for a brain tumor)
- Surgical destruction of the pituitary or the blood vessels or nerves leading to it

Signs and Symptoms

Symptoms of hypopituitarism depend on hormones that are lacking, and may contain short stature, intolerance to colds, fatigue, infertility, and failure to produce breast milk. Although the symptoms sometimes start suddenly and intensely, but they usually develop progressively and may not be recognized for a long time. The symptoms depend on which pituitary hormones are insufficient. In some cases, the production of a hormone in the pituitary is reduced. More typically, the levels of several hormones decline simultaneously (pancreatic hypofunction) [55].

Growth Hormone Deficiency

The deficiency of growth hormone (GH), in children, usually leads to short stature (*dwarfism*), and poor overall growth. In adults, growth hormone (GH) deficit does not affect height because the bones are fully grown. Adults usually have no symptoms, but sometimes they lose energy.

Hypothalamus Deficiencies

The hypothalamus is the brain's small part situated near the pituitary gland. It produces hormones and nerve impulses regulating the pituitary gland. Therefore, tumors affecting the hypothalamus may cause pituitary hormone deficiency. They can also interfere with the center of appetite control, leading to obesity.

Prolactin Deficiency

The ability of women to produce breast milk after delivery is reduced or lost as a result of prolactin deficiency. Sheehan syndrome (a rare birth complications) is one of the reasons for low levels of prolactin and other pituitary hormones. Sheehan syndrome is usually developed due to excessive loss of blood and shock during childbirth, leading to partial damage of the pituitary gland. The symptoms of prolactin deficiency include fatigue, loss of pubic and mane hair, and incapability to make breast milk. Prolactin deficiency has no adverse effects on men.

Deficiency of Gonadotropins (FSH and LH)

In premenopausal women, the lack of these hormones can lead to stoppage of menstrual periods, infertility, vaginal dryness, and loss of certain feminine sexual features. In men, these hormonal deficiencies lead to testicular weight loss (atrophy), erectile dysfunction, reduced sperm production, secondary infertility, and loss of certain male sexual features. In children, the lack of these hormones can lead to delayed puberty. Lack of LH and FSH may also occur in Kallmann's syndrome, in which a person may also have a cleft palate, color blindness, and no odor.

Pituitary Apoplexy

Pituitary apoplexy or stroke is a group of symptoms caused when blood flow to the pituitary is blocked leading to tissue destruction and bleeding. Pituitary apoplexy is most common in people with pituitary tumors. Symptoms include severe headaches, visual field defects, fever, stiff neck, and eye movement problems. Bleeding causes the pituitary to swell and compress the hypothalamus, causing drowsiness or coma.

The pituitary gland may abruptly stop producing hormones, especially adrenocorticotropic hormone, which leads to low blood pressure and low blood glucose levels [55].

Pancreas Related Disorders

Diabetes Mellitus

Diabetes is the most prevailing endocrine disorder and characterized by a group of disorders summarized as hyperglycemia (high blood sugar levels) [58]. Metabolic syndromes such as diabetes are caused by an imbalance in insulin, synthesized by the pancreatic beta cells. Islets of Langerhans are responsible for the production of beta cells. Insulin plays a significant role in the absorption and use of glucose [59]. Abnormal beta cell function leads to a deficiency in insulin and amylin ultimately increasing the diabetic patients' body weight [60]. Hepatocyte nuclear factor 4-alpha (HNF4A) is accountable for pancreatic beta cell's gene transcription, where liver genes play a crucial role. In patients with type 2 diabetes, there is a trend of heterogeneity, non-ketosis and non-functionality of 2–5% of beta cells [61]. Even though mutations in the liver gene may progress to maturity-onset diabetes in younger people, yet this is non-insulin-dependent diabetes [62]. GDM usually occurs during pregnancy and mother as well as newborn are at high risk [63].

Clinically, diabetes is characterized by high levels of blood sugar and imbalances in lipid and carbohydrate metabolism. Untreated diabetes can cause hyperglycemia. For the diagnosis of diabetes, fasting blood glucose >140 mg/dL (>7.7 mmol/L) or random blood glucose levels >200 mg/dL (>11.1 mmol/L) are threshold values. Glycated hemoglobin's % age (also known as glycosylated hemoglobin or HbA1c) is usually used to measure diabetes control in patients because this percentage is related to the average blood glucose level within 3 months. Poor long-term glycemic control often causes microvascular complications in various organs of the body including kidneys, eyes, heart, and nervous system. Diabetic patients are always at a higher risk of coronary heart disease and infection complications [64].

Signs and Symptoms

Recently diabetes is being classified on the basis of pathological processes involved in the insulin secretion and resistance. There are three main types of diabetes, i.e., type 1 diabetes, type 2 diabetes, and gestational diabetes mellitus (GDM). Type 1 diabetes and type 2 diabetes may arise at any age. Type 1 diabetes patients need insulin regularly, while type 2 diabetes patients do not need daily insulin. Gestational diabetes is a state in which pregnant women have elevated blood sugar and may think that there may be no diabetes. Sometimes, it continues even after childbirth. There is a great risk of type 2 diabetes and cardiovascular disease development in females having a history of GDM [65]. In type 2 diabetes, insulin antagonism can

lead to multiple genetic deformities such as c-cleft, cleft lip, and neural tube defects. Genetic factors, weight, and age are also major risk factors for diabetes. Diabetes can lead to nocturnal hypoglycemia, and brain damage in severe cases [66].

Diabetes can be treated by ingesting a drug that contains an alpha-glucosidase inhibitor, or by maintaining proper diet and exercise [67]. There is a new mechanism named pressure reflex, which causes an enhanced morbidity and mortality in patients with diabetes by altering heartbeats [68]. Insulin resistance also interferes with lipid metabolism, increasing fatty acids leading to obesity, type 2 diabetes, and cardiovascular disease [69]. Chronic complications of diabetes, due to changes in minerals and bone metabolism, may cause bone loss [70]. Diabetic patients also experience macrovascular and microvascular problems. Major vascular complications include coronary heart disease, peripheral vascular disease, and cerebrovascular disease, while the effect on small blood vessels, capillaries, small arteries, and venules are microvascular complications [64]. Microvascular complications are more common in adults and the elderly, but rarely in children and adolescents [71]. The classic clinical indicators of diabetes are called three P's which are polyuria, polyphagia, and polydipsia. As the level of glucose in the blood rises, the kidney's function to reabsorb glucose is compromised, causing glucose spill in the urine and hence leading to osmotic diuresis. Usually glucose is not detected in the urine, so if there is any glucose present in the urine, it is an abnormal phenomenon. Weight loss, fatigue, blurred vision, and thirst may also occur.

Hypoglycemia

Hypoglycemia is a common endocrine disorder related to diabetes. Blood glucose levels <60 mg/dL (3.3 mmol/L) are referred to as hypoglycemia. Here average blood level values are mentioned but these levels may vary from individual to individual. In general, when plasma glucose levels fall below 60 mg/dL (3.3 mmol/L), a rapid and continuous cascade of actions start as follows:

1. The body will reduce insulin secretion to prevent a drop in blood sugar levels.
2. Next, the secretion of counter-regulatory hormones, mainly adrenaline and noradrenaline, is increased.
3. At the end, signs and symptoms, including cognitive decline, become obvious. When the glucose level drops below 50 mg/dL (2.8 mmol/L), there are significant mental state alterations.

If hypoglycemia is not treated, there will be more morbidity and mortality rate. To reduce these risks, timely identification of signs and symptoms and quick and affective treatment is required. Hypoglycemia in insulin-dependent diabetes mellitus is usually results from taking high insulin dose, eating very less, or sometime both. Central nervous system's tissues are different from other tissues as they can metabolize protein or fat, usually including sugar, and rely completely on glucose as their energy source. If the level of glucose in the blood drops sharply, the brain will be factually starved. Hypoglycemia in patients without a history of diabetes is referred

to as *fasting or postprandial hypoglycemia*. Fasting hypoglycemia results from an imbalance between glucose production and utilization. Postprandial hypoglycemia is considered by hyperinsulinemia in the diet, often seen in patients undergoing gastric surgery. Many conditions can trigger fasting hypoglycemia, but most common are severe enzyme deficiency, pancreatic tumors (e.g., insulinoma), severe infections, liver disease, and drug overdose (e.g., insulin, sulfonylureas). Clinical features are similar to those of diabetic hypoglycemia [72].

Signs and Symptoms

The clinical precipitations of hypoglycemia typically develop rapidly. Patients will strive for the treatment of variety of signs and symptoms directly linked with the release of endocrine stress hormones, including sweating, cold, pale, sticky skin, tremors, and tachycardia. If you do not treat hypoglycemia, you may experience mental status changes and generalized seizures. It is essential to check the blood glucose of each active seizure patient to rule out hypoglycemia. Hypoglycemia refers to a blood glucose level of <70 mg/dL, but the medical history of patient, gender, age, and overall health may change the absolute level of signs and symptoms. Elder people having a complex medical history may experience severe hypoglycemia when glucose levels are >50 mg/dL (>2.8 mmol/L). However, young adults may experience severe hypoglycemia, which is quite below 50 mg/dL (<2.8 mmol/L). Many clinical signs of hypoglycemia occur by the production of counter-regulatory hormones (such as epinephrine), secreting in response to decrease glucose concentrations [73].

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is associated with a plasma glucose concentration >350 mg/dL (>19.4 mmol/L), ketone production, serum bicarbonate levels <15 mEq, and anion gap metabolic acidosis. DKA has a mortality rate of 9–14%. It is an acute endocrine disorder where insulin insufficiency and elevated glucagon levels together lead to hyperglycemia, volume depletion, and acidosis. This situation is usually associated with electrolyte imbalance. Certain metabolic stress factors (e.g., infection, trauma, myocardial infarction, and sometimes even pregnancy) may cause DKA. A common trigger in these situations is usually the disruption of insulin therapy in diabetic patients. Lack of insulin inhibits glucose from entering the cell, so cells are unable to metabolize cellular functions due to lack of glucose and switch to other sources of energy, such as fat. Consequently, glucose tends to accumulate in the blood [74].

The flow of glucose into the renal tubules pulls water, potassium, magnesium, sodium, and other ions into the urine, producing an important osmotic diuretic effect. This diuretic effect, along with vomiting, can lead to electrolyte imbalance, volume depletion, and subsequent shock. All such changes in permeability are the

main cause of the decline in the mental state of DKA patients and are more risky for children. Metabolic acidosis is a clinical symbol of DKA. Physiologically, the human body tries to recompense and remove acid by using deep and fast breathing, a process known as Kussmaul's respiration, and attempting to consume more bicarbonate. Potassium is transported into the blood in acidosis, which is transferred in the kidneys by osmotic diuresis. This process leads to pseudohyperkalemia or the initial high blood levels, which can quickly become hypokalemia by DKA treatment [75].

Signs and Symptoms

DKA patients become sick after dehydration. They usually report polyphagia, polydipsia, and polyuria. Patients with severe DKA will show a change in mental status during the initial investigation. There may be tachycardia, shortness of breath, and changes in body position. In addition, etco2 will be low, depicting the presence of metabolic acidosis in DKA. Signs and symptoms of DKA include [76]:

- Abdominal pain (especially common in children)
- Nausea and vomiting
- Fatigue and weakness
- Fruity breath odor
- Tachypnea/hyperpnea
- Orthostatic hypotension
- Increased diuresis
- Hemodynamic shock in severe cases
- Altered LOC
- Cardiac dysrhythmia
- Seizures

Hyperosmolar Hyperglycemic Nonketotic Coma

Hyperosmolar hyperglycemia nonketotic coma (HHNC) is a severe diabetes complication. It has 10–50% mortality rate. It is hard to distinguish DKA from HHNC but we can find it by checking patient's medical history, raised blood sugar levels, and a lack of low etco2. Usually patients with type 2 diabetes develop HHNC and it is elicited by the same stressor that causes DKA. This condition has the following characteristics:

- Raised plasma glucose concentration, usually >600 mg/dL (>33.3 mmol/L)
- Increased serum osmolality, usually >315 mOsm/kg
- Lack of ketone production

HHNC is accompanying with substantial dehydration and decreased mental status. Sometimes it develops into a complete coma. Compared with DKA, acidosis

Table 1.3 Common causes and signs and symptoms of HHNC

Causes	Signs and symptoms
Trauma, drugs, myocardial infarction, Cushing's syndrome, sepsis, cerebrovascular accident (stroke), dialysis, CNS insult (e.g., subdural hematoma), hemorrhage, pregnancy	Fever, dehydration, vomiting and abdominal pain, hypotension, tachycardia, rapid breathing, thirst, polyuria or oliguria, polydipsia, focal seizures, altered LOC, focal neurologic deficits

and ketosis usually do not exist in this case, so etco2 does not decrease. It should be noticed that other factors, such as potential sepsis and respiratory dysfunction, can alter etco2 [77].

HHNC has a complex pathophysiology yet similar to DKA. This situation usually does not arise suddenly, but will last for a few days. The length of time depends on the overall health of the patient. HHNC usually occurs in the elderly and in patients who are weak due to comorbidities. The major effect in HNNC is a decrease in insulin action, which stimulates a large counter-regulation mechanism that increases serum glucose. Once insulin function declines, glycogen breakdown (release of glucose stored in glycogen form), gluconeogenesis (internal manufacture of glucose inside the body), and reduction in peripheral glucose absorption will predominate. After that fluid is drawn into the extracellular space due to hypoglycemia, stimulating osmotic diuresis, ultimately causing hypotension and volume deficiency. The patient is initially able to maintain the vascular volume by a continual fluid intake, but the diuretic will eventually exceed the system. Remember that other conditions, such as sepsis, can lead to further exhaustion of capacity [78] (Table 1.3).

Conclusion

In this chapter the basic physiology of endocrine system including glands and their respective hormones is summarized. All endocrine glands produce one or more hormones which regulate many body functions and maintain homeostasis inside the body. All of these hormones play crucial role in many body functions and the over and under secretion of any of these hormones may lead to several metabolic disorders. Some of these metabolic disorders are life threatening so a balance should be maintained in these hormonal secretions. Most of endocrine hormones are regulated by a negative feedback mechanism to keep these hormonal secretions in check. But sometimes due to some problem in the negative feedback mechanism of endocrine hormonal secretion, any damage to endocrine gland, endocrine gland's tumor, infection, disease, or a genetic disorder may cause hormonal imbalance leading to several metabolic disorders.

Conflict of Interest The authors declare that they have no conflicts of interest.

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Chapter 2
Impaired Carbohydrate Metabolism in Metabolic Disorders

Hina Sharif, Kanwal Rehman, Muhammad Sajid Hamid Akash, Kanwal Irshad, and Ghulam Murtaza

Abstract Metabolic disorders, also known as inborn errors of metabolism, are a group of inherited genetic disorders due to enzymatic deficiency caused by some defective genes. There are over 600 genetic metabolic disorders discovered so far, many of them are present in newborns or after a short time thereafter. People affected with these disorders often remain asymptomatic and healthy for even years. The symptoms usually start appearing when the metabolism undergoes some stress conditions as in prolonged fasting or in febrile illness. Metabolic disorders due to impaired carbohydrate metabolism are usually a result of deficiency of some enzymes which are involved in the normal metabolic pathways of carbohydrates. They are mostly autosomal recessive disorders. This chapter deals with the normal metabolic pathways of fructose, galactose, and glycogen and some common metabolic disorders which are caused by the enzyme deficiency required for the metabolism for these carbohydrates.

Keywords Inborn metabolic disorders · Galactosemia · Essential fructosuria Hereditary fructose intolerance · Glycogen storage diseases

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Introduction

Metabolism is the net result of all the biochemical processes occurring in living organisms that involve the conversion of food into smaller particles and the production of energy which is required for the structural and functional purposes vital to sustaining life [1]. Metabolic processes may be catabolism which refers to the degradation of macromolecules to yield simpler ones with the production of energy [2] or anabolism which refers to the biosynthesis of macromolecules by consuming energy, e.g., lipids, proteins, DNA, RNA, etc. [3]. Every metabolic pathway is dependent on some specific enzymes and certain substrates for its smooth functioning [4].

Metabolic disorders can be defined as inborn errors of metabolism caused by deficiencies of certain enzymes that are involved in the metabolism of proteins, lipids, or carbohydrates. The enzyme deficiency is because of the inherited gene mutations for the respective enzyme [5]. More than 600 genetic metabolic disorders have been identified so far and all presenting different signs and symptoms, many of them are present in newborns and maybe within a short time after birth [6]. Such metabolic disorders are referred to as inborn errors of metabolism (IEM). Genetic deficiency of catalytic enzymes in the metabolic pathways is the main reason for IEM, but cellular process abnormalities which involve cell signaling, transmembrane transport, cell differentiation, and production of energy also contribute a lot [1]. Such disorders are although rare, but collectively they can lead to childhood disability and deaths. Many of them are autosomal recessive disorders [7].

Carbohydrate, being the essential component of our diet, provides almost 50% of energy from total dietary energy intake. Endogenous reserves in the body such as liver glycogen and muscles are also the sources of carbohydrates. The dietary carbohydrates comprised monosaccharide as fructose, glucose, and galactose, disaccharides as sucrose, maltose, and lactose, and polysaccharides as starch, among these the starch and sucrose constitute the major portion of dietary carbohydrates [8]. Carbohydrate metabolism involves the digestion of dietary carbohydrates in the gastrointestinal tract and results in the breakdown of complex molecules into monosaccharides which is then transferred to the cells via glycolysis, pentose phosphate pathway, and Krebs cycle for aerobic and anaerobic respiration. Figure 2.1 is a schematic representation of all biochemical pathways happening in cytoplasm and mitochondria [9].

Metabolism of carbohydrates provides elements for nucleic acids which constitutes its functional role and also provides a major source of energy. Impaired carbohydrate metabolism occurs due to the disruption in the metabolic pathway of carbohydrates which results in metabolic disorders [10]. The disorders of carbohydrate metabolism can be categorized as follows.

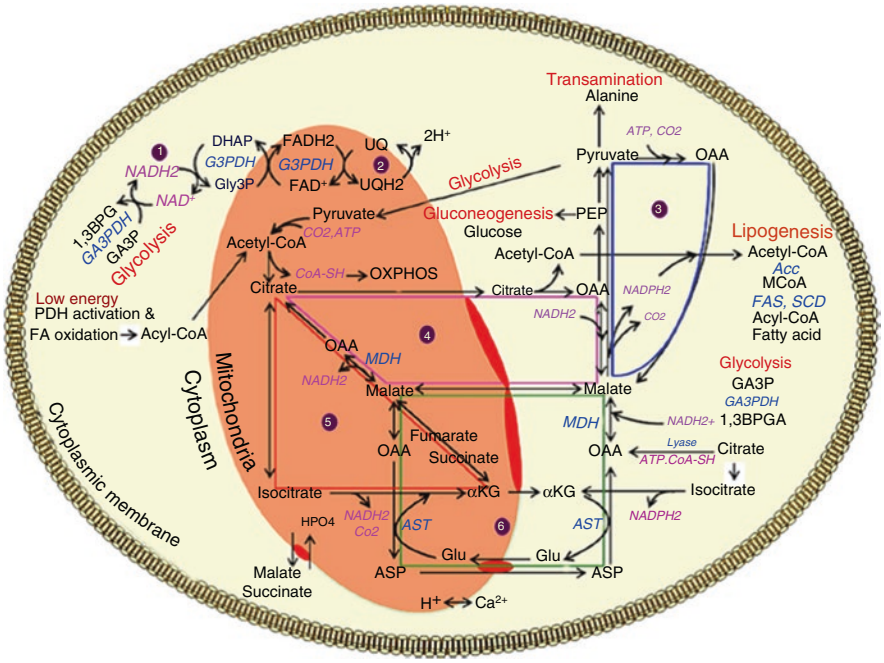

Fig. 2.1 Presentation of metabolic pathways happening inside the cytoplasm and mitochondria 1-Glycerol phosphate shuttle, 2-NADH shuttle into IMM, 3-transhydrogenase cycle, 4-Citrate cycle, 5-TCA cycle, 6-malate-aspartate shuttle. Adopted from ref. [9]. *ACC* acetyl coenzyme-A carboxylase, *ADP* adenosine diphosphate, *Asp* aspartic acid, *AST* aspartate aminotransferase, *ATP* adenosine triphosphate, 1,3-*BPGA* 1,3-biphosphoglyceric acid, CO_2: carbon dioxide, *DAP* dihydroxyacetone phosphate, *DHAP* dihydroxyacetone phosphate, *FAD* flavin adenine dinucleotide, $FADH_2$: reduced flavin adenine dinucleotide, *FA-oxi* fatty acid oxidation, *GA3P* glyceraldehyde-3-phosphate, *GA3PDH* glyceraldehyde-3-phosphate dehydrogenase, *G3PDH* glycerol-3-phosphate dehydrogenase, *Glu*: glutamic acid, *IMM* inner mitochondrial membrane, *α-KG* alpha-ketoglutarate, *α-KGDH* alpha-ketoglutarate dehydrogenase, *MCo-A* malonyl coenzyme-A, *MDH* malate dehydrogenase, *NAD+* nicotinamide adenine dinucleotide, *NADP* nicotinamide adenine dinucleotide phosphate, *NADPH* nicotinamide adenine dinucleotide phosphate hydrogen, *OAA* oxaloacetic acid, *OXPHOS* oxidative phosphorylase, *PDH* pyruvate dehydrogenase complex, *PEP* phosphoenolpyruvate, *SCD* stearoyl coenzyme-A desaturase, *UQ* ubiquinone, UQH_2 ubiquinol

Metabolic Disorders Induced by Impaired Galactose Metabolism

Lactose, a disaccharide consisting of galactose and its 4′-epimer glucose, is present in human milk, cow's milk, and in some infant formulas [11]. Metabolism of galactose is carried out in the Leloir pathway [12] which has three main enzymes galactokinase (GALK), galactose-1-phosphate uridyltransferase (GALT), and UDP-galactose 4′-epimerase (GALE) [13]. A schematic representation of the Leloir pathway of galactose metabolism has been shown in Fig. 2.2 [12]. Due to hydrolysis, ingested lactose is converted into glucose and galactose via lactase enzyme in

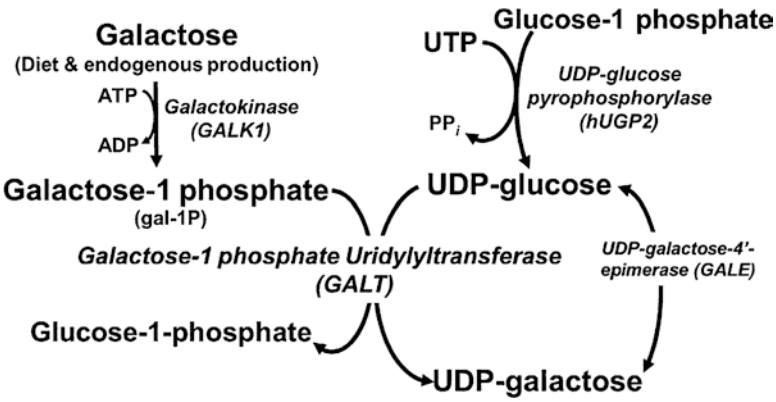

Fig. 2.2 Schematic representation of the Leloir pathway of galactose metabolism. *ATP* adenosine triphosphate, *ADP* adenosine diphosphate, *UDP* uridine diphosphate, *PPi* inorganic pyrophosphate, *GALK* galactokinase

the small intestine. By the metabolic process, galactose is converted into galactose-1-phosphate which is then combined with uridine phosphoglucose to form uridine diphosphogalactose and glucose-1-phosphate (G1P). The deficiency of each of these enzymes results in disorders of galactose metabolism, galactosemia being the most common and severe disorder among them [13]. Galactosemia results from the failure in the metabolism of galactose [14]. It is an autosomal recessive disorder, and has three forms depending upon the deficiency of an enzyme involved [10].

Classic Galactosemia

This disorder is the manifestation of deficiency of GALT enzyme which occurs because of the gene mutations of the GALT enzyme, hence leading to the accumulation of metabolites of galactose metabolism that are galactitol and galactose-1-phosphate [10]. Galactose-1-phosphate can accumulate in all tissues and inhibit other enzymes too as phosphoglucomutase and glucose-6-phosphate dehydrogenase [14]. Newborn infants with classic galactosemia show normal weight at birth but their weight shows a decline as they start feeding [15]. Newborns with this disorder are asymptomatic but as they are exposed to milk, life-threatening symptoms start appearing which include difficulties in feeding, renal tubular dysfunction, hypoglycemia, hepatomegaly, vomiting, diarrhea, and cataracts. Speech difficulties, cognitive disabilities, visual perceptions, hypergonadotropic hypogonadism, and reduced bone mass are the long-term complications [8]. The mortality rate of classic galactosemia is 1 in 40,000 to 60,000 newborns [15]. Immediate restriction of galactose containing foods is a primary treatment of classic galactosemia. Instead of this, soy milk, amino acids-based formulas, or formulas with other carbohydrate sources are preferred [10].

GALE Deficiency Galactosemia

This condition is extremely rare showing the same clinical presentations like that of GALT deficiency including vomiting, jaundice, and hepatomegaly. GALE deficiency causes the accumulation of galactitol and galactose-1-P [15]. Newborns having a severe deficiency of GALE enzyme must be on diet excluded from lactose but in most cases do not require a restriction of galactose [13].

Cataracts

A progressive opacity of the lens is termed as cataracts which result from molecular damage [16]. GALK deficiency is the leading cause of cataracts showing no damage to the kidney, liver, and brain, though GALK deficiency can lead to pseudo-tumor cerebri in some cases. Due to this enzyme deficiency, phosphorylation of galactose into galactose-1-phosphate is inhibited which results in the accumulation of galactose and galactitol, the latter is accumulated in the lens leading to osmotic swelling of lens fibers and hence protein denaturation [13, 17]. Exclusion of diet containing lactose is the primary intervention for its treatment [13].

Metabolic Disorders Induced by Impaired Fructose Metabolism

Fructose is a major sweetening agent in a human diet which may be in free form as in honey, some fruits, and in many vegetables or maybe a disaccharide as sucrose which consists of glucose and fructose. Sorbitol is also a source of fructose present in some fruits and vegetables [18]. Fructose and glucose are being used in many metabolic pathways including glycolysis, Krebs cycle, glycogenolysis, gluconeogenesis, pentose phosphate shunt, and Cori cycle [19]. Fructose metabolism undergoes in the liver, renal cortex, and mucosa of small intestine catalyzed by fructokinase, aldolase B, and triose-kinase [18]. By phosphorylation process catalyzed by fructokinase, fructose is converted into fructose-1-phosphate, which is then split into two compounds dihydroxyacetone phosphate (DAP) and triose glyceraldehyde, the reaction being catalyzed by fructose-1-phosphate aldolase. DAP then undergoes glycolytic pathway, whereas glyceraldehyde can undergo three metabolic pathways (a) phosphorylated to glyceraldehyde phosphate by the action of triose-kinase, (b) oxidized to glycerol by glycerol kinase, and (c) oxidized to glyceric acid and then phosphoglycerate by the action of glyceric acid kinase [20]. Three inborn disorders have been identified from impaired fructose metabolism caused by the deficiency of its three enzymes that include essential fructosuria, hereditary fructose intolerance, and the fructose-1,6-biphosphatase deficiency [18].

Essential Fructosuria

It is an autosomal recessive, benign, and mostly asymptomatic metabolic disorder caused by the deficiency or complete lack of fructokinase enzyme, leading to increased blood levels of fructose after taking diet having sucrose or fructose and almost 10–20% of fructose is excreted unchanged via renal excretion [21, 22]. Patients with this disorder remain unidentified for a long time and hence have a normal life expectancy [22]. Dietary restriction of fructose is not indicated for its treatment as it is a rare non-disease [18].

Hereditary Fructose Intolerance

This disorder is the manifestation of the deficiency of enzyme aldolase B, affecting the liver, kidney, and small intestine, presenting with symptoms of hypoglycemia, vomiting, nausea, lethargy, and abdominal pain and eventually coma, convulsions, and jerks. The renal tubule is the principal target of the noxious effect of fructose [18, 23]. Patients with this disease exhibit normal health and remain asymptomatic unless they are not exposed to a fructose-containing diet [18]. Infants on breastfeed develop normally with this disorder as human milk lacks fructose, whereas those on formulas containing fructose from the first day of life do not thrive normally, lose weight, become dehydrated and often develop hepatomegaly and most often die within the first month of their life [22]. When a patient is suspected of hereditary fructose intolerance, it is recommended to eliminate fructose from diet. Intensive care and supportive therapy as fresh frozen plasma are needed in acute cases [18].

Fructose-1,6-Phosphatase Deficiency

It is not an impaired fructose metabolism, rather a disorder of gluconeogenesis, an autosomal recessive disorder caused by a mutation in the FBPI gene. Newborns having this disorder may present with hypoglycemia and lactic acidosis and then maybe clinically silent [24]. In the acute cases, the symptoms may progress to irritability, coma, dyspnea, tachycardia, apneic spells, hypotonia, and hepatomegaly. Due to impaired gluconeogenesis, glucose formation is inhibited which results in hypoglycemia [18]. It is a very rare condition having a mortality rate of 1 in 350,000 cases [24]. Intravenous or oral administration of glucose is recommended for the treatment of this disorder, and avoidance of fasting for maintenance therapy [18].

Metabolic Disorders Induced by Impaired Glycogen Metabolism

Glycogen, also known as animal starch, is a high molecular weight polysaccharide, containing up to 10,000 glucose residues [25]. It is actually a mobilized storage form of glucose in the liver and skeletal muscles that can provide energy by degrading into glucose residues [26]. The glucose units in the structure of glycogen are bonded via α-1,4-glycosidic bonds in linear chains and at branches via α-1,6-glycosidic linkages [27]. Glycogenesis, a metabolic pathway of glycogen synthesis, is regulated by hormone insulin and catalyzed by glycogen synthase enzyme [28], whereas glycogenolysis is a metabolic pathway of glycogen degradation, modulated by glucagon hormone, occurring in liver and muscles for balancing of blood sugar level and provision of energy. The process of glycogenolysis is catalyzed by glycogen phosphorylase [9].

Glycogen Storage Diseases

Glycogen storage diseases (GSDs), also known as glycogenosis, are a group of inherited disorders affecting glycogen metabolism. Liver and skeletal muscles being the major organs for the metabolism of glycogen are also affected [10, 29]. GSDs are caused by genetic deficiencies in the enzymes which are involved in the metabolic pathways of glycogen, resulting into abnormal amount and/or structure of glycogen [30]. They are autosomal recessive disorders. GSDs are numbered in accordance with their discovery and they were considered similar in pathology but later on they were appeared not to be similar in pathology. GSDs having a lower number have a severe end of the spectrum, whereas those having a greater number show severe fasting intolerance [31]. The initial treatment in all types of GSDs involves the immediate correction of hypoglycemia [32].

GSD Type 0

It is a rare disorder that occurs due to the deficiency of glycogen synthase which is required for glycogen synthesis. After consuming carbohydrates, glycogen is not formed from glucose which leads to postprandial hyperglycemia and hyperlactatemia. Its clinical presentations are pallor, lethargy, nausea, vomiting, and convulsions in some cases [33]. Children in infancy with this disorder are usually asymptomatic. This is the only type of GSD which is not associated with hypoglycemia and hepatomegaly as it causes a decrease in liver glycogen. This disorder is caused by a mutation in the glycogen synthase 2 gene [34].

GSD Type I

It is, also known as von Gierke's disease, the most common hepatic GSD having a mortality rate of 1/100,000 in a live birth. Glucose-6-phosphatase deficiency is its leading cause, the enzyme necessary for the conversion of G6P to glucose and Pi [35]. This enzyme is necessary for the catalysis of the last step in both glycogenesis and glycogenolysis. Due to this enzyme deficiency, G6P accumulates leading to enhanced lactate production [31]. It has further two subtypes, GSDIa caused by a mutation in the subunit G6Pase-alpha and is a true enzyme defect and GSDIb due to the defect in G6P translocase and a transport defect. Hypoglycemia, hepatomegaly, hyperlipidemia, and lactic acidosis are common clinical presentations [31, 35]. The symptoms usually appear during infancy [36].

GSD Type II

This disorder, also known as Pompe disease, is caused by acid-α-glucosidase [37] which leads to lysosomal glycogen accumulation in skeletal muscles, smooth muscles, heart, and in the nervous system [38]. It is a serious and fatal disorder. It is also termed as progressive neuromuscular disorder and can occur at any age and have a mortality rate of 1 in 40,000–600,000. GSD type II is also associated with cardiac hypertrophy and hepatomegaly. Infants with this disease often fail to achieve developmental milestones like standing, sitting, and walking due to loss in muscle strength [39].

GSD Type III

GSD type III, also known as Cori's disease, is caused by a deficiency in glycogen debranching enzyme (GDE) which is involved in glycogenolysis [40]. Due to this enzymatic deficiency glycogen accumulates in the muscles and liver [41]. The major complication of this disorder is hypertrophic cardiomyopathy [42]. In 85% of cases, the activity of GDE is absent in both liver and skeletal muscles and in 15% of cases, only the liver is involved [43]. Hypoglycemia, cirrhosis, hyperlipidemia, ketosis, myopathy, and hepatosplenomegaly are its common clinical presentations. At adolescence, hypoglycemic effects decrease but exercise intolerance and cardiomyopathy worsen [10, 44].

GSD Type IV

It is, also known as Anderson's disease or amylopectinosis, a rare autosomal disease, which results from the deficiency in glycogen branching enzyme (GBE) which causes accumulation of abnormal glycogen amylopectin which is a plant starch [45]. It is caused by a mutation in the GBE1 gene. Clinical presentations include hepatosplenomegaly, failure to thrive, muscular atrophy, hypotonia, cardiopathy,

myopathy, exercise intolerance, and cirrhosis. Death can occur in early childhood [10, 46].

GSD Type V

It is, also known as McArdle disease, the most common skeletal muscle disorder [46]. It is an autosomal recessive disorder that is caused by a deficiency in enzyme myophosphorylase (muscles phosphorylase). This enzyme liberates glucose in skeletal muscles from glycogen [47]. In this disease, muscles are unable to use glycogen during the physical activity in the initial phase. At the later phase, due to increased blood supply patients can function normally, this is termed as "second wind" phenomenon [10]. Exercise intolerance which includes myalgia, muscle contractures, painful cramps, premature fatigue and myoglobinuria is its clinical presentation.

GSD Type VI

It is, also known as hers disease, a very rare disorder caused by a deficiency of liver phosphorylase which is required for glycogenolysis [40]. Hepatomegaly is the only clinical symptom [36]. It occurs due to mutation in the PGYL gene [10].

GSD Type VII

It is, also known as Tarui disease, due to deficiency of phosphofructokinase. Exercise intolerance, myopathy, muscle cramps, hemolysis, hyperuricemia, and myoglobinuria are its clinical presentations [46]. It is clinically similar to GSD type V [10].

GSD Type VIII

This disorder, the mildest form of GSDs, is caused by a phosphorylase enzyme deficiency which is required for the hydrolysis of glycosidic linkages α1-4 and α1-6. This results in an accumulation of glycogen in the liver [48]. Hepatomegaly and CNS degeneration in early childhood are common symptoms. This disorder shows no hypoglycemia and is fatal in childhood [36].

GSD Type IX

This disorder is caused by a deficiency of phosphorylase kinase enzyme. It has two subtypes, type IXa which is an autosomal recessive trait and type IXb which is a sex-linked recessive trait. There is no hypoglycemia in this disorder [36]. Hepatomegaly and fasting ketosis are its clinical presentations [10]. When hepatomegaly occurs in

Table 2.1 types of GSDs and their signs and symptoms

Types	Common names	Enzyme deficiency	Signs and symptoms
GSD 0	–	Glycogen synthase	Hypoglycemia, hepatomegaly
GSD I	Von Gierke	Glucose-6-phosphatase	Hypoglycemia, hepatomegaly, hyperlipidemia, lactic acidosis
GSD II	Pompe	Acid maltase	Cardiomegaly and hepatomegaly
GSD III	Cori	Glycogen debranching enzyme	Hypertrophic cardiomyopathy, hypoglycemia, cirrhosis, hyperlipidemia, ketosis, myopathy, hepatosplenomegaly
GSD IV	Anderson	Glycogen branching enzyme	Hepatosplenomegaly, failure to strive, muscular atrophy, hypotonia, cardiopathy, myopathy, exercise intolerance, cirrhosis
GSD V	McArdle	Myophosphorylase	Exercise intolerance
GSD VI	Hers	Liver phosphorylase	Hepatomegaly
GSD VII	Tarui	Phosphofructokinase	Exercise intolerance, hemolysis, hyperuricemia, myoglobinuria
GSD VIII	–	Phosphorylase	Hepatomegaly, CNS degeneration
GSD IX	–	Phosphorylase kinase	Hepatomegaly and fasting ketosis

CNS central nervous system, *DAP* dihydroxyacetone phosphate, *DNA* deoxyribonucleic acid, *FBP* fructose-1,6-biphosphatase, *G1P* glucose-1-phosphate, *G6P* glucose-6-phosphate, *GALE* UDP-galactose 4'epimerase, *GALK* galactokinase, *GALT* galactose-1-phosphate uridyltransferase, *GBE* glycogen branching enzyme, *GDE* glycogen debranching enzyme, *GSDs* glycogen storage diseases, *GYS* glycogen synthase, *HFI* hereditary fructose intolerance, *IEM* inborn errors of metabolism, *PGYL* phosphorylase glycogen liver, *RNA* ribonucleic acid, *UDP* uridine diphosphate

this disorder then symptoms usually appear in early childhood. Children with this disorder are shorter than normal and their puberty is often delayed [49]. Table 2.1 summarizes types of GSDs, their common names, and causes along with their signs and symptoms.

Conclusion

Metabolic disorders, being more complex and fatal, should be monitored closely especially in newborns having these disorders. Carbohydrates represent the essential component of the diet for our body so the impaired metabolism of carbohydrates is the subject of ongoing research for understanding in a better way the underlying causes of metabolic disorders caused by impaired fructose, galactose, and glycogen metabolisms.

Conflict of Interest There is nothing to declare.

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Chapter 3
Mitochondrial Dysfunction in Metabolic Disorders

Ghulam Murtaza, Muhammad Tariq, and Ramzi Shawahna

Abstract Mitochondria are the energy houses of cells. Cell functioning and stability are critical responsibilities of mitochondria. The other functioning of cells includes ATP production, intracellular calcium ion regulation, production of reactive oxygen species, radical scavenging property, regulation of the cell survival and death, and caspase family of protease stimulation. Mitochondrial dysfunction can be described as abnormality in functioning in addition to the production of reactive species. Mitochondrial dysfunction leads to the development of metabolic syndromes such as obesity, diabetes, and neurodegenerative disorders. Since the past, many studies have been done on morphology, physiology, and pharmacology of mitochondria involved in metabolic diseases. By adopting interventions that include lifestyle intervention, pharmacologic approaches, and the targeted-mitochondrial methodologies, the progression of metabolic disease decelerates. These approaches are involved in maintaining mitochondrial number and morphology, eliminate dysfunctional mitochondria, and reduce oxidative stress in metabolic disorders. The aim of the study is to illuminate the role of mitochondria in the metabolic disorder and sum up the process of the targeted mitochondrial molecule to treat metabolic syndrome.

Keywords Mitochondria · Metabolic disorders · Oxidative stress

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Introduction

Mitochondria are rod-shaped organelles found intracellularly. Mitochondria are also known as the driving force of cell because it produces most of the energy supply of cells in the form of adenosine triphosphate (ATP) and also plays a dynamic part in metabolizing nutrients. There are many other cell functions performed by mitochondria like energy metabolism along with the production of ion radicals, homeostasis, and cell integrity [1, 2]. Mainly, glucose is oxidized to produce ATP via OXPHOS and also the metabolites of Kreb's cycle and fatty acid are also oxidized to produce ATP. Presently, it is now a well-known fact that pathophysiological changes produced in mitochondria in metabolic disease are directly linked with decreased mitochondrial working with the time as age increases, the biogenesis of mitochondria is decreased which may be due to changes in pattern of segregation and merging of mitochondrial cells and inhibiting the process of mitophagy. In this process, the dysfunctional mitochondria are removed [3]. The reactive oxygen species belong to a free radical family, it includes O^{2-}, OH^{-}, and peroxyl [4]. Mitochondrial cells have many defense processes to pledge the production of ROS, as it is a predictable process and can be held whenever generated. This overproduction of reactive oxygen species causes the DNA, lipids, and proteins to degrade to some extent [2]. Oxidative stress is a risk factor for several diseases, including cancer, diabetes, stroke, aging, and neurodegenerative diseases [5]. There are various pathophysiological conditions that emerge due to oxidative stress which is related to metabolic disorders [5].

Metabolic syndrome is a cluster of health issues that include obesity, diabetes, and dyslipidemia. These conditions increased the risk of elevated blood glucose level, heart and blood vessel diseases. In this modern era, it may be the major health issue of this society. Metabolic syndrome has several causes that act together like overweight and obesity. Also, other factors involved in metabolic diseases are social, personal, and economic burden [6]. From previous studies, it was evident that environmental factors and genetic variability participate in increasing the situation of metabolic syndrome [7]. There are numerous data available that proves the role of mitochondrial dysfunction and aging in the pathophysiology of aging, neurodegenerative disorder, and metabolic disease [5]. However, the basic mechanism of metabolic syndrome still remains unknown. This review article basically focused on the mode of action involved in mitochondrial abnormality and the link between this abnormality and the metabolic syndrome. So that the pharmacologic actions were taken to target dysfunctional mitochondria to prevent the health hazards associated with a metabolic disorder.

Functional and Dysfunctional Mitochondria

Mitochondria are cytoplasmic membranous organelle; it has its own self-replicating genome. Mitochondria play a vital role in maintaining metabolic homeostasis and are mediators of cell integrity. The energy produced by mitochondria in eukaryotes

is by oxidation of NADHA/$FADH_2$ via glycolysis. In addition to glycolysis, other mechanisms are also involved in generating NADH2/FADH2; these are the TCA cycle, oxidative phosphorylation, and β-oxidation of fatty acids. These processes are controlled by transcription factors present in mitochondria and there are about 800–1000 copies of mtDNA present in the single mitochondrion that is inherited and packaged in nucleoids [8]. However, nucleoids are widely spread in the matrix of mitochondria but mostly reside in the vicinity of cristae. Cristae is an organelle that carries the OXPHOS system. Between inner and outer membrane there is a small space present which is called intermembrane space. The outer and intramembranous space of mitochondria has more penetration power than the inner membrane. The permeability of the inner membrane is low because the inner membrane has enzymes that perform the ETC process to generate ATP. The mitochondrial matrix is surrounded by a mitochondrial membrane where the TCA cycle produces electrons that are taken up by ETC to produce ATP. The OXPHOS process is derived through the production of electrochemical gradient across the inner membrane [9].

The electron transport chain contains five subunits of enzyme complexes. These are complex I (NADH ubiquinone reductase), complex II (succinate dehydrogenase), complex III (Ubiquinol-cytochrome c reductase), complex IV (cytochrome c oxidase), and complex V (F_0F_1 ATP synthase). They are located in the inner mitochondrial membrane [10]. Electrons are donated by the TCA cycle which then travel to the electron transport chain. These electrons travel from enzyme complex I to V. Transport of protons is also coupled with the transfer of electrons along the ETC that generate electrochemical gradient which produces ATP [11]. Mitochondria continuously produce reactive species by metabolizing oxygen. The electron flow through the electron transport chain is an imperfect process. Mitochondria consume incompletely reduced oxygen and produce reactive species such as ($\bullet O^{-2}$) which is also called "Primary" ROS [12]. The secondary ROS is also generated due to the excessive generation of primary ROS [13]. It has been proved that the deoxyribose, backbone of DNA, i.e., a nitrogenous base, purine and pyrimidine, damages due to the interlinking of hydroxyl radical with DNA [2]. The increased production of reactive species causes damage in mitochondrial proteins/enzymes, DNA, and other cell structures as a result of an abnormality in mitochondrial functioning and failure to produce ATP in mitochondria [12]. The electron transport chain also generates other reactive species of nitrogen. Nitration induced by reactive nitrogen species is affected by cellular proteins and glutathione. Similarly, free radicals which are produced freely can also inhibit the oxidative damage both by enzymatic and non-enzymatic mechanism. The mechanisms involved can scavenge free radicals by antioxidants or lead to generation of free radicals.

The oxidative stress which is produced by increased release of free radicals can be overcome by several defense mechanisms. The following are involved in enzymatic defense mechanism such as SOD, CAT, GR, and GPx. Similarly, the non-enzymatic defense system possesses antioxidant compounds such as Vitamin C and E, glutathione, etc. The ionic imbalance produces damage in the cells which causes other abnormalities to appear in the cell including impairment of enzymatic functions which further degrade the mitochondrial function [5]. In diabetes, the number

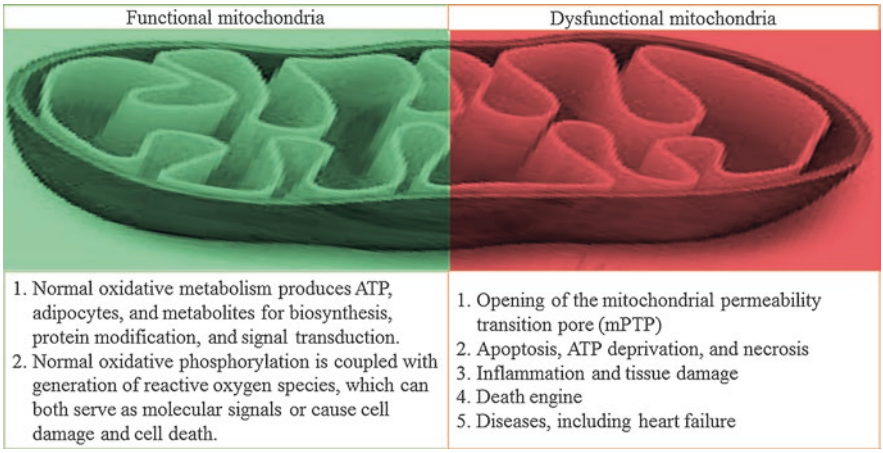

Fig. 3.1 Mechanisms involved in functional and dysfunctional mitochondria

and functioning of mitochondria are reduced by reducing oxidative phosphorylation [14]. In mammalian cells, as a key regulator of body functions, neurodegenerative disorders occur even due to minute change in mitochondria [15]. Figure 3.1 represents the mechanisms involved in functional and dysfunctional mitochondria.

Mechanisms Controlling Mitochondrial Replication

Mitochondria in combination with nuclear and mitochondrial genome maintain its physiology and morphology with the help of various transcription factors. These transcriptional factors include nuclear respiratory factor, mitochondrial transcriptional factor A, PPARs, uncoupling proteins, estrogen and its related factors α and γ [16], Tfam, NRF, and NRF-2. To maintain the integrity of mitochondria, various stimuli are involved, which may be pathological and physiological. In combination with the above compounds, co-transcriptional regulatory factors are also involved in regulating a number of mitochondria. Physical exercise, dietary changes, and muscle movements are also the stimuli that contribute to maintaining the number of mitochondria. These transcriptional factors interact with co-transcriptional factor Peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1α (PGC-1α) to control the transcription of the main enzyme in mitochondria and also synthesize mtDNA [17]. In the case of low energy, along with transcription factors, there are two more enzymes to compensate for the low energy state, these include AMP-activated protein kinase and mammalian counterpart of silent information regulator 2. These are also called as metabolic sensors. In the case of low energy state, the AMP activates protein kinase phosphorylate and mammalian counterpart of silent information regulator 2. In a low energy state, AMPK phosphorylates and SIRT1 acetylates to regulate PGC-1α [18]. The role of PGC-α and other transcriptional

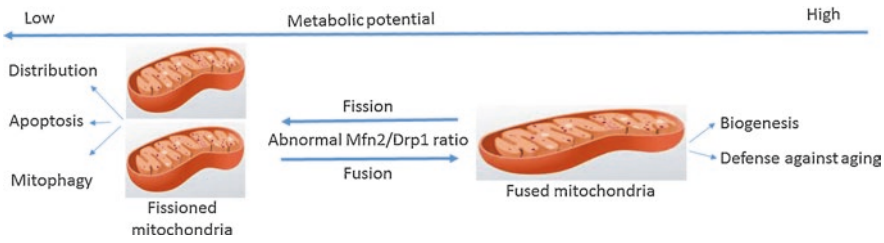

Fig. 3.2 A schematic representation of mitochondrial dynamics (fusion and fission). Mitochondrial fusion involves the coordinate merging of the two outer membranes and the two inner membranes

factors is well-portrayed in literature. It has been proved in many studies that due to pathologic conditions changes occur in morphology and number of mitochondria in different body organs such as heart and skeletal muscles [1].

Fission and Fusion Balance of Mitochondria

Mitochondria host the process of fission and fusion and its balance, the balance between these two processes is called mitochondrial dynamics (Fig. 3.2). Mitochondrial dynamics are involved in maintenance during cell growth and cell death and its pathway and also eradicate the worn-out mitochondria [19]. This process was explained for the first time when the yeast was budded [20].

The shape and size of mitochondria fluctuate frequently due to external stimuli which may include the number of nutrients and others. Mitophagy is a process in which mitochondria fuse with lysosomes via fusion and remove the dysfunctional mitochondria; in other words, it is an autophagy-lysosomal system [21]. When the amount of nutrients increases from its demand and cellular dysfunction worsens, it causes mitochondrial fragmentation and increases the risk of metabolic diseases [22]. The impairment of mitochondria causes the failure of oxidative capacity which results in overproduction of reactive oxygen species. Since the past, many kinds of literature have been documented giving us the data of regulators involved in fusion and fission. The mitochondrial fusion process is controlled by three GTPase, these are mitofusin 1 and 2 and optic atrophy1 [23]. The outer membrane of mitochondria holds Mitofusin 1 and Mitofusin 2, while the inner one holds OPA 1. While on the other hand fission is regulated by two GTPase genes, FIS 1 (on the outer membrane of mitochondria), and Drp 1(on outer membrane and cytosol). The fusion process works by intermixing of mitochondrial content and maintaining the electrical conductivity [24]. When normal functioning of mitochondria is disturbed by diminishing fusion or fission process which results in increased generation of reactive species, the enzyme activities alter in mitochondria, decreased in calcium balance (homeostasis), inhibition of production of ATP and low energy metabolism. The studies earlier have proved that changes occur in mitochondria due to increasing metabolic and neurodegenerative disorders [25].

Oxidative Damage to Mitochondria Triggering Its Dysfunction

The imbalance between two antagonistic forces is referred to as oxidative stress which causes the production of ROS and minimizes antioxidants. It is also a well-known fact that the damaging effect of reactive oxygen species is more as compare to compensatory. Mitochondrial dysfunction is a series of events that occur in mitochondria which involve dysfunction in mitochondrial biogenesis, changes produced in the membrane potential, and the decrease in size, number, and oxidative proteins of mitochondria [26]. In the body, it is a routine process of generating reactive oxygen species by oxygen metabolism in which mitochondria have the lead role in generating these reactive species [12]. These reactive species when interacting with other cellular components like DNA, protein, lipids, etc. in the OXPHOS process result in mitochondrial dysfunction [27]. Metabolic syndrome involves many diseases such as hypertension, obesity, hyper-dyslipidemia, and others. Changes in mitochondrial functions increase the risk of diseases like diabetes, obesity, dyslipidemia, and cardiovascular diseases. The abnormal cell metabolism causes the irregular generation of energy and its consumption, which are the main cause of metabolic syndromes [28]. Morphological changes occur due to enhanced glucose levels and increased reactive species [29]. When the signaling pathway of insulin is inhibited it causes the accumulation of fatty acids and lipids which can also be the reason for metabolic syndrome [30]. The following data, mentioned in Fig. 3.3, give us a detailed discussion about the connection between metabolic disorders and mitochondrial dysfunction.

Mitochondrial Involvement in Obesity

Presently, obesity has a strong impact on our society and is a major health issue worldwide. It is the main health issue created due to metabolic syndrome and also linked with other risk factors associated with other diseases. There are many factors that involve in generating obesity such as environmental and genetic factors. Mitochondrial dysfunction is also the cause of obesity. As explained from studies the NADPH oxidase and anti-oxidative enzymes in obese mice have declined due to

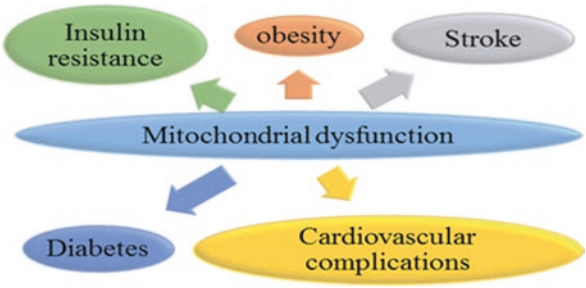

Fig. 3.3 Various diseases in which mitochondrial dysfunction is involved

increased release of reactive oxygen species in adipose tissues [31]. Interestingly, it has also been documented that abdominal obesity is generated by mitochondrial dysfunction such as in rodents and humans [32]. The gene expression is also reduced in an obese person. So, the obesity can be linked with gene expression of mitofusin 2 lost in skeletal muscle, the mitochondrial dysfunction starts in the tissue [33].

Mitochondrial Involvement in Insulin Resistance

When the level of insulin attains lesser response by cells, the condition is termed as insulin resistance. There are many factors that contribute to insulin resistance which include increased age, decreased physical exercise, obesity, and tension. So, it can say that oxidative stress in mitochondria may be the reason for insulin resistance [1]. Though it is still not confirmed that metabolic diseases such as insulin are caused by mitochondrial alterations or disorder, many studies have documented this fact that alteration in mitochondrial number and morphology cause to generate insulin resistance in skeletal muscle [34]. When glucose level increases from its demand the reactive species of oxygen also increases which causes mitochondrial alterations [29]. Similarly, when insulin signaling pathways inhibited, it causes accumulation of fatty acids and lipids which results in the generation of metabolic syndrome [30]. In various studies, mitochondrial metabolism markers have altered in the person who is insulin resistant. From the data, it is found that mitochondrial changes in skeletal muscle cause the increase in deposition of lipids and develop insulin resistance. It is also a well-known fact that lesser fatty acid oxidation results in stopping insulin signaling which leads to free fatty acid and insulin resistance and also decreases oxidation and ATP production in these individuals [29]. However, advance researches are needed to describe the mitochondrial function and insulin sensitivity via the antioxidant pathway.

Mitochondrial Involvement in Diabetes

Since the past, there is an increased incidence of type 2 diabetes and this number has become a major problem worldwide. Now diabetes increases up to 382 million individuals and this number is increasing rapidly. Many factors are involved in diabetes but still, the main reason is not clear. Myocytes, adipocytes, and hepatocytes are the insulin-sensitive cells when get resistant they are called insulin resistant along with that abnormal functioning of pancreatic cells is also the main factor that contributes to insulin resistance. Now, recent studies have proved that the involvement of mitochondrial abnormal functioning causes an excess of reactive species which induce diabetes [29]. T2DM is the outcome of lesser tissue sensitivity and secretion of insulin [35, 36]. recent study was done on diabetic and obese patients showed decreased glucose production and impaired lipid homeostasis in skeletal muscle [35]. In obese

persons, the fat mass causes low glucose transport, stops insulin to perform its action, and increases FFA and others [37]. The hyperglycemic condition develops when the glucose level rises from its range and insulin sensitivity decreases [38]. In a diabetic person, at cellular level mitochondrial respiration and its density decrease which also decreases the energy production in the form of ATP and mRNA. Insulin resistance and type 2 diabetic patients at the cellular level have reduced mitochondrial respiration, ATP production and mitochondrial density and mRNA [39]. Oxidative stress always increases with the intake of the high-calorie diet which causes OXPHOS to increase its enzyme protein expression. In the brain, the increase in reactive oxygen species in the OXPHOS process is the major cause of oxidative damage of mtDNA [40]. When the insulin signaling pathway is inhibited by an excess of reactive species and also interferes with acetyl CoA to being oxidized in obese and diabetic persons results in increased lipid and diacylglycerol [1]. In diabetic and obese conditions, mitochondrial synthesis has impaired [35]. PGC-1α also involved in the generation of mitochondria [41]. In addition, mitochondrial dysfunction may be the target of therapeutic measures to treat diseases such as obesity and diabetes.

Mitochondrial Involvement in Cardiovascular Complications

Heart diseases are also a major issue around the globe. There are many factors which are involved in cardiovascular diseases, these are an environmental and genetic factor. From studies, it is confirmed that oxidative stress is directly proportional to an increased number of mtDNA. The heart can generate many reactive species in the heart cells including cardiac myocytes, endothelial cells, and neutrophils. There are many in vivo and in vitro researches available that documented that oxidative stress has a high impact on reducing reactive species in the cells [6]. The reactive species in the heart are generated when ETC complexes I and III get disrupted [42]. In accordance with this, other mechanisms are also involved in damaging heart tissues by producing reactive oxygen species, these are NADPH oxidase, xanthine oxidoreductase, or NOS. The increased reactive oxygen species decreases the antioxidant capacity of cell and causes cell injury which results in an alteration in gene expression, damaging mtDNA and abnormality in the functioning of endothelial cells [6], this results in failing heart muscle called myocardium [43]. Additionally, reactive oxygen species activate contractile functions, activate enzymes and transcription factors. Thus, the reactive oxygen species could be involved in cardiovascular diseases.

Mitochondrial Involvement in Stroke

Stroke is the main cause of death in developing countries. There are many factors that induce a stroke. They may be economical, physiological, or others. Among these, oxidative stress is also the contributing factor which causes a stroke by tissue

injury [44], this oxidative stress then evolves abnormality in mitochondria, so mitochondrial dysfunction is also indirectly the cause of brain stroke. As the mitochondrial disorder causes decreased supply of oxygen and glucose to the tissues, it decreases the production of ATP and also the pathway of cell death change [45]. There are a series of experimentation done on the stroke model, to generate a stroke model the oxygen supply of the stroke model is stopped and also the glucose source is terminated which results in decreased oxidative metabolism. There are series of events generated in a nutrient-deprived stroke model which causes high storage of reduced material and accumulation of reactive oxygen species [44]. The tissue damage starts in the form of necrosis and apoptosis when the heart muscle gets focal ischemia due to oxidative stress [46, 47]. Thus, peroxynitrite radical is the causative agent of brain stroke. Thus it is proved that in the ischemic brain, oxidative metabolism is the result of the overproduction of reactive species brain [45].

Concluding Remarks

Mitochondria, the membranous organelle is involved in cell death and survival [47]. The main functions of mitochondria include the production of energy. Also, it hosts many cellular functions including metabolism of energy, generation of reactive species, and Ca^{2+} homeostasis along with cell integrity. Alteration in the morphology and function of mitochondria produces metabolic disorders in humans. Mitochondrial dysfunctions in metabolic syndrome that were reported in recent studies were impaired dynamics of mitochondria, deformity of synthesis of mitochondria, abnormal functioning of mitochondria, and production of reactive oxygen species. Furthermore, the researchers showed that maintaining mitochondrial dynamics and functions is mandatory to treat metabolic diseases. If we want to slow down the progression of metabolic disease, many interventions and approaches are helpful to make life better. These include lifestyle intervention, pharmaceutical plans to treat the patient in better ways, and mitochondrial-targeted molecules for the treatment of patients. However, the link between metabolic syndrome and mitochondrial function has not been fully elucidated. Similarly, genetics and its susceptibility with metabolic syndromes and the role of epigenetics are unclear. Additionally, the treatments related to metabolic syndromes are not so beneficial as the body physiology varies from population to population.

Conflict of Interest Nothing to declare.

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Chapter 4
Inherited Metabolic Disorders: A Current Status

Muhammad Shahid, Arslan Rasool, and Fozia Anjum

Abstract Inherited metabolic diseases (IMDs) are heterogeneous group of diseases that are mostly monogenic in nature. IMDs are caused by the genetic mutation in the enzyme activity results in accumulation of progressive intoxication compounds which ultimately leads to cell dysfunction or cell death. The clinical results of inherited metabolic diseases are severe that ultimately leads to death. In the past there are limited therapeutic measures available which are used for the treatment of inherited metabolic diseases including enzyme replacement therapy, and chaperone technology. Recent studies in the disciplines of molecular genetics, biochemistry, and cell biology have emerged many novel technologies in medicines including gene therapy, gene editing, cellular therapies, and organ transplantation provide potential treatment against these diseases. Main genetic defects cannot be fully cured by current therapies but these are helpful to overcome the metabolic problems. Further studies are required to make these therapeutic measures more efficient so that families get benefit that are affected by these in born errors of metabolism.

Keywords Inborn errors of metabolism · Inherited metabolic disorders · Hematopoietic stem cell transplantation · Enzyme replacement therapy · Gene therapy

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Introduction

Inherited metabolic diseases (IMDs) are the large class of genetic disorders caused by disruption of normal metabolic processes or by genetic mutations. Genes that code the protein may be enzymes of metabolic processes affected by mutation and results in loss of ability to provide normal products. IMDs do not include diseases which are affected by modifications in structural proteins, membrane proteins, signal transduction between cells, transcription factors, and by hormone synthesis. These consequences are also known as inborn errors of metabolism in which enzymes are unable to perform normal body function. Many babies affected by IMDs seem to be normal at birth but they show neurological signs and symptoms in childhood. This disease causes mental retardation that leads to the death of newborns [1]. There are different types of pathomechanisms which are affected by partial or complete loss of enzymatic activity that leads to various metabolic disorders. These include:

- Metabolites and toxic substances are accumulated
- Non-metabolized substrate is accumulated
- Deficiency of biochemical product
- Overproduction of biochemical product
- Insufficient production of ATP

There are many therapies that are used for the treatment of inherited metabolic diseases. The well-known techniques used for the treatment of IMDs are recombinant enzyme replacement (ERT) therapy and hematopoietic stem cell transplantation (HSCT). These techniques are used to replace the defected genes to perform normal metabolic process. However, limitations are applied to these therapies. Moreover, the ERT is unable to cross blood–brain barrier and proved to be ineffective against neurological disorders [2]. So, other techniques like chaperone technology, gene therapy, and administration of ERT in spinal canal via injections in order to make it more useful are under investigation [3].

Inheritance and Nosology of Inborn Metabolic Diseases

In 1902, Archibald Garrod was an English physician first discussed the inborn errors of metabolism (IEMs) [4]. Most of the IEMs are autosomal recessive having two defective genes in order to develop symptoms for the trait or disorder. More than six hundred or seven hundreds of IEMs have been discovered since then [5]. In case of autosomal dominant disease, there is only one defected gene present to develop a disease [6].

Nosology refers to the classification of disorders [7]. There are hundreds of inherited metabolic disorders caused by different genetic defects [8]. The largest classes of inherited metabolic diseases are given in Table 4.1.

Table 4.1 Major classes of inherited metabolic diseases (IMDs)

Disorders	Examples
Disorders of carbohydrates metabolism	Galactosemia, glycogen storage diseases
Disorders of amino acid	Alkaptonuria (AKU), Phenylketonuria (PKU), Homocyteinuria
Lysosomal storage disorders	Lysosomal storage diseases
Disorders of purine and pyrimidine metabolism	Lesch-Nyhan syndrome (LNS)
Disorders of peroxisomal function	Zellweger syndrome
Disorders of steroids metabolism	Congenital adrenal hyperplasia
Disorders of mitochondria	Kearns-sayre syndrome
Disorders of porphyrins	Acute intermittent porphyrias

Disorders of Carbohydrates Metabolism

Galactosemia

In 1908, von Ruess an European scientist first described the galactosemia belongs to the class of disorders in carbohydrate metabolism. Galactosemia is a rare genetic disorder in which patient's body become unable to metabolize blood galactose into monosaccharides [9]. In young mammals this is more significant because the main disaccharide in milk is lactose which is hydrolyzed into glucose and galactose, respectively. Galactosemia in its severe condition can affect many organs including brain and cause mental retardation. The disease can also cause life threatening conditions and lose of ability of many tissues to perform its function [10].

There are three types of inherited galactosemia. Type I galactosemia is classic galactosemia which is caused by deficiency in enzyme activity of galactose-1-phosphate uridylyltransferase (GALT) [11]. Type II galactosemia and type III galactosemia caused by deficiency of enzyme galactokinase (GALK) and galactose epimerase (GALE). Classic galactosemia is an autosomal recessive disease and more than three hundred variations have been discussed in GALT enzyme [12].

Main Pathway of Galactose Metabolism

Galactose metabolism pathway is also known as Leloir pathway named after Luis Federico Leloir in which α-D-galactose is metabolized by three enzymes in three steps as shown in Fig. 4.1.

- In first step, α-D-galactose is metabolized by GALK into galactose-1-phosphate.
- Secondly, GALT converts galactose-1-phosphate and UDP-glucose into α-D-glucose-1-phosphate and UDP-galactose.
- In the last step, GALE is required for interconversion of UDP-galactose into UDP-glucose.

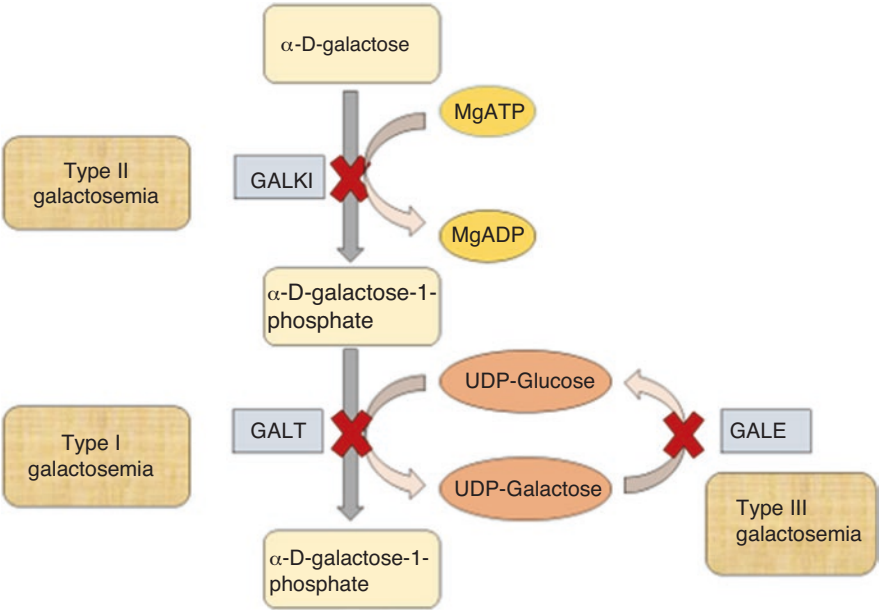

Fig. 4.1 Leloir pathway for metabolism of galactose. First step involve the phosphorylation of α-D-galactose into α-D-Galactose 1-phosphate catalyzed by galactokinase (GALK). Inhibition of GALK results in type II galactosemia. In second step, UDP glucose reacts with α-D-Galactose 1-phosphate to form α-D-glucose 1-phosphate and UDP-galactose catalyzed by galactose 1 phosphate uridylyl transferase (GALT). Inhibition of GALT results in type I galactosemia. Galactose epimerase (GALE) is responsible for the interconversion of UDP-Galactose to UDP-Glucose. Deficiency of this enzyme results in type III galactosemia. This enzyme also catalyzed the interconversion of UDP-N-acetyl galactosamine to UDP-N-acetyl glucosamine in mammals to maintain cellular UDP-sugar which are used in the synthesis of conjugated molecules like glycolipids and glycoproteins

Treatment of Galactosemia

Galactosemia can be controlled by adopting a healthy life style and controlled diet. Foods that are rich in galactose like dairy products are not given to the patients that are suffering from galactosemia. However, the diet plan can be vary depending upon the severity of the disease. Some of them are prescribed to take less fruits and vegetables as they contain small amount of galactose. During ripening of fruit, some plants secrete galactose in alpha and beta forms so that the quantity of galactose increases in fruits [13]. Fermented fruits like soy sauce, miso, etc. are avoided for galactosemia patients. List of food containing galactose contents is given in Table 4.2 [14]. Moreover, the young ones that are suffering from galactosemia have deficiency of soya proteins. So, calcium and vit D tablets are recommended for those in which these minerals and vitamins are deficient [15]. Some metabolic foods which are helpful to avoid accumulation of toxic substances in the body can also be used for the treatment of galactosemia [16].

Table 4.2 List of food products containing galactose contents

Sr.#	Food items rich in galactose	Food items with low galactose content	References
1-	Dairy-based products	Hydrolyzed vegetable protein	[14]
2-	Jarlsberg	Soy milk	
3-	Gruyere	Grated 100% Parmesan cheese	
4-	Plant-based products	Breast milk, all milk-based infant formulas	
5-	Cheddar cheese	All milk-based ingredients including, casein	
6-	Legumes	Sodium and calcium caseinate	[15]
7-	Garbanzo beans	Organ meats, meat-by-products	[13]
8-	Fruit and vegetable juices	lso fermented soy sauce that has not been fermented is made from hydrolyzed soy protein	

Disorders of Amino Acid

Phenylketonuria

Phenylketonuria is an autosomal recessive disorder first reported by Ivar Asbjørn Følling in 1934. It belongs to IEMs which is caused by genetic defect in phenylalanine hydroxylase enzyme [17]. Phenylalanine is converted into tyrosine in the presence of phenylalanine hydroxylase (PAH) in which tetrahydrobiopterin works as a cofactor. Deficiency in the activity of PAH enzyme results in the accumulation of toxins in brain along with the increased level of phenylalanine in the body. The symptoms of phenylketonuria appears as the child grow includes intellectual disability, psychiatric symptoms, mental retardation, seizures, and behavior problems [18].

Molecular Genetics and Classification

There are 13 exons and their regulatory introns are present on PAH gene. The inheritance pattern of phenylketonuria is autosomal recessive. It means PKU is developed when mutation occurs in both of their alleles. The mutation can be occur either in the promoter region or in any exons and intervening introns [19]. Classification of PKU depends upon the concentration of phenylalanine in the blood as shown in Table 4.3. Hyperphenylalaninemia is condition in which concentration of blood phenylalanine is abnormally elevated from the normal concentration that is 50 to 110 μmol/L [20].

Table 4.3 Classification of phenylketonuria based on phenylalanine concentration in blood

Types of hyperphenylalaninemia (HPA)	Phenylalanine (PKU) concentration in blood (μmol/L)	Symptoms	Reference
Mild HPA	Less than 600	Intellectual impairment	[20]
Mild PKU	600–1200	• Seizures, • Tremors • Eczema	
Classical PKU	Above 1200	Neuropsychiatric complications	

Treatment

Glycomacropeptide

The cheese whey contains a protein known as glycomacropeptide that have high amount of essential amino acid except aromatic amino acids [21]. When diet is prepared for patients, it is ensured that it should be free from phenylalanine and then glycomacropeptide can be added into it. Studies suggested that diet which contains glycomacropeptide gives satisfactory results by the patients suffering from PKU [22].

Tetrahydrobiopterin (BH4)

Patients suffering from mild phenylketonuria have genetic defects in the production of tetrahydrobiopterin (BH4). Doses of tetrahydrobiopterin increases the activity of PAH enzyme results in decreased level of blood circulating phenylalanine up to desire limit [23]. For the treatment of PKU patients, some neurotransmitter precursors like carbidopa and hydroxy-tryptophan are also used [24].

Lysosomal Storage Disorders

Lysosomal storage diseases (LSDs) belong to the inherited disorders of metabolism and were first described in 1972 [25]. Lysosomes are the cellular organelles that are involved in the digestion or engulfing of foreign particles (bacteria and viruses) and catabolic reactions of dead and wastes products of cells like polysaccharides, lipids, and proteins. There are more than sixty different types of acidic hydrolases including sulfatases, lipases, nucleases, proteases, and phosphatases that are involved in catabolic reactions. Lysosomal storage diseases are the inborn errors of metabolism that disrupt the activity of lysosomes [26].

Genetics

Lysosomal storage disorders consist of more than 70 genetic disease that are monogenic (controlled by 1 gene) in nature. They can be inherited as autosomal recessive disorders. Only 3 of them inherited as X linked diseases [27]. LSDs are caused when genetic mutation is occurred in those genes that codes for lysosomal proteins like proteases, activators, transporters and lipases, etc. These mutations can defect the functioning of lysosomes that results in accumulation of wastes and toxins in the cell and ultimately cause cell death [28].

Treatment

There are some therapeutic measures that can be used for the treatment of lysosomal storage disease. The mutated enzyme can be treated by enzyme replacement therapy (ERT), while the accumulation of substrates in the lysosomes can be decreased by using substrate-reduction therapy [29]. Chaperone therapy is used to increase the functioning of mutated enzyme. Other treatments like gene therapy can also be used for their treatment but there are many LSDs that cannot be fully cured by these therapies [30]. Some of the recommended FDA approved drugs are given in Table 4.4.

Disorders of Purine and Pyrimidine Metabolism

Lesch–Nyhan Syndrome

Lesch–Nyhan disease is a rare X-linked recessive disorder of purine metabolism caused by the defect in hypoxanthine guanine phosphoribosyl-transferase (HGPRT) enzyme which is used in salvage pathway as shown in Fig. 4.2. In 1964, this disease was first described by W. Nyhan and M. Lesch who observed unusual symptoms in

Table 4.4 FDA of approved drugs for the treatment of selected Lysosomal storage disease

isorder	Approved drug	Production site	Therapy type	References
Gaucher disease	• Imigluceras • Velaglucerase alfa • Taliglucerase alfa	• Secreted from chinese hamster ovary (CHO) cells • Produced in Human cells • Produced in plant cells	• Recombinant enzyme	[29]
Fabry disease	• Agalsidase beta • Agalsidase alfa	• Produced in CHO cells • Produced in human cells	• Recombinant enzyme • Chaperone therapy	
Pompe disease	• Alglucosidase alfa	• Produced in CHO cells	• Recombinant enzyme	

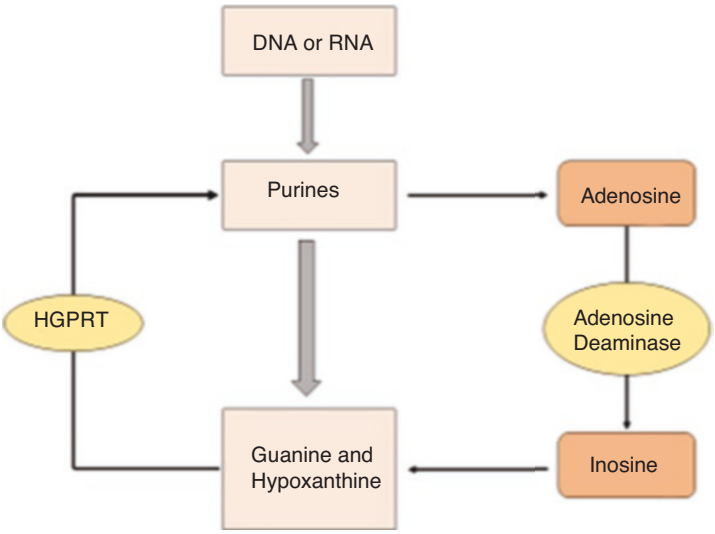

Fig. 4.2 Purine salvage pathway. In this pathway, free purine and pyrimidine bases are converted into nucleotides. These free bases are the intermediates of DNA or RNA in degenerative pathways. HGPRT is a transferase that catalyzes conversion of hypoxanthine to inosine monophosphate and guanine to guanosine monophosphate

two brothers. They showed severe symptoms of choreoathetosis, self-harm, dystonia, and urine crystals [31]. A complete description of inheritance pattern of LNS and elevated level of uric acid found in patients by examining the lost activity of HPRT enzyme in RBCs. After five decades, it becomes a standard which is used to diagnose the HPRT activity in RBCs in Lesch–Nyhan syndrome [32].

Genetics

LNS is an inborn error of metabolism having lost enzymatic activity caused by the mutation in gene present on the chromosome Xq26 [31]. This genetic mutation is present in newborn babies by birth [33]. Deficiency in the activity of HPRT results in hyperuricemia that accumulate in the body and causes delayed growth, mental retardation, arthritis, muscle weakness, and gout [34].

Treatment

There are several therapeutic measures that have been used to cure the deficiencies of LNS. Allopurinol drug is useful for the treatment of gout. It prevents muscle weakness and renal failure in babies which is major cause of death and increases their life span [35]. Moreover, these drugs are unaffected against mental retardation and neurological disorders of LNS [36]. Self-injury or self-harm behavior can be treated by using benzodiazepines, anti-convulsive drugs, neuroleptics, and

chloral-hydrates [37]. Latest therapeutic measures include botulinum toxin A that influence CNS and PNS, gabapentin and dopamine therapy [38].

Disorders of Steroids Metabolism

Congenital Adrenal Hyperplasia (CAH)

There are a number of disorders such as CAH which are inherited from patients due to enzymatic dis-functioning involved in the biosynthesis of cortisol. Adrenal cortex hyperplasia results when the level of ACTH and corticotrophin releasing hormone elevated as a negative feedback of pituitary gland and hypothalamus due to over production of cortisol. The disorders resulting from enzymatic imbalance or lower production may include stoppage of an individual pathway or multiple activities. It is recorded that almost 90% of the cases of CAH are caused by the lower production of steroid 21 hydroxylase [39]. On the basis of cortisol there are two forms of 21-OH deficiency, namely classic and non-classic. Depending upon their bad effect in infants to cause spontaneous hypotensive crisis 21 OHD is also divided into groups such as simple virilizing and salt wasting [40].

Genetics

Hyperplasia includes all those types which are autosomal recessive and monogenetic disorders but lethal. In most of the cases almost all the patients have altered sequence of alleles encoding for a specific gene product. Medically, those alleles are preferred which give more relationship among genotype-phenotype and functional enzymes [41]. The synthesis of steroids from cholesterol occurs in adrenal glands in many steps catalyzed by enzymes. The process of steroidogenesis is disturbed due to deficiency of many enzymes leading to congenital adrenal hyperplasia of many types. There is another pathway which is termed as androgen biosynthesis that occurs in gonads and it may also lead to pathophysiology of congenital adrenal hyperplasia. Medical symptoms of congenital adrenal hyperplasia are found to be more closely related to disability. Their clinical findings are shown in Table 4.5.

Treatment

Glucocorticoid Replacement

Glucocorticoid replacement is required in patients associated with 21OHD chronic disease. Hydrocortisone is used for the children before their complete growth because they act in a short period of time. It is not clear yet that their specific concentration in a day has significant benefit or not [44]. Growth suppression can be

Table 4.5 Clinical features and genetic causes in congenital adrenal hyperplasia

Enzyme deficiency	Gene	Hormonal profile	Treatment	References
21-hydroxylase deficiency	*CYP21A2*	• High level of 17OHP, 21-deoxycortisol, and rostenedione and renin • Low level of Cortisol and aldosterone • Suppression of elevated adrenal steroids after glucocorticoid administration	Sodium-chloride supplementation Vaginoplasty and clitoral recession or clitoroplasty with preservation of neurovascular bundle in female DSD Glucocorticoid-administration	[42]
11β-hydroxylase deficiency	*CYP11B1*	• High level of DOC, 11-deoxycortisol, and rostenedione • Low level of aldosterone, corticosterone	Glucocorticoid-administration Vaginoplasty and clitoral recession or clitoroplasty with preservation of Neurovascular bundle in female DSD	
17α-hydroxylase/ 17,20-lyase deficiency	*CYP17*	• High level of DOC, progesterone and corticosterone • Low level of Cortisol 17OHP, renin, androstenedione and DHEA	Glucocorticoid-administration Surgical correction of genitalia and sex hormone replacement in male DSD consonant with sex of rearing sex hormone replacement in females	[40]
3β-hydroxysteroid dehydrogenase type 2 deficiency	*HSD3B2*	• High level of DHEA, 17-hydroxypregnenolone and renin • Low level of progesterone, 11-deoxycortisol, androstenedione and Cortisol	Glucocorticoid-administration Sodium-chloride supplementation	
P450 oxidoreductase deficiency	*POR*	• High level of Progesterone, DOC, corticosterone and Pregnenolone • Low level of androstenedione and DHEA	Glucocorticoid-administration	[43]
Lipoid congenital adrenal hyperplasia or SCC enzyme deficiency	*StAR*	• High level of Renin • Low level of All steroids	Gonadectomy of male DSD sex hormone replacement consonant with sex of rearing	

avoided by using low concentration of doses [45]. Hydrocortisone can be used for treatment in adults but synthetic glucocorticoids are more efficient.

High potency drugs including dexamethasone and prednisolone show some side effects like sleeplessness, mild mood change, fluid retention, and weight gain [46]. Patients suffering from classic 21OH deficiency should be treated by stress dose of steroid in pregnancy and delivery cases [47]. Women treated with glucocorticoids have less ratio of pregnancy loss as compared to those which are suffering from non-classic 21OH deficiency. Due to this reason, glucocorticoids proved useful during gestation and pregnancy period [48]. Men suffering from testicular adrenal rest tumors (TARTs) needed 1 dose of glucocorticoid that helps in suppression of adrenocorticotropic hormone (ACTH) [49].

Mineralocorticoid Replacement

For the treatment of patients with 21OH deficiency, mineralocorticoid replacement is essential. It is dire need for the infants which are associated with this disease severely that they should be treated with high doses of mineralocorticoid and supplements should be given in addition to sodium chloride. Level of mineralocorticoid is not maintained in adults because there is over 21 hydroxylation of progesterone released from adrenal [50]. The level of ACTH and vasopressin decreases in response to recovery of normal amount of blood and mineralocorticoid replacement which leads to decrease in the required concentration of glucocorticoid essential for the optimum working of androgen secretion [51]. Fludrocortisone doses are used to maintain the blood pressure while sitting and standing as well as to maintain the normal range of plasma renin activity [52].

Conclusion

Nosology for IMDs provides an overview for recognized IMDs grouped based upon their molecular genetics and etiology. In last few decades, improved technologies for sample analysis and gene sequencing have accelerated the research in the field of IMDs. Our understanding of the genetic basis, pathophysiology, management, and improved detection methods has increased substantially in recent years. Many diseases are well characterized at their gene levels and provide potential treatment against these disorders. Significant advances in enzyme replacement therapy, gene therapy, and stem cell technology have resulted in increased survival rate. Although there are many treatments available for neurological conditions but research is in continuous progress. It is encouraging that studies are still required to understand and treatment for these diseases. Further genetic and biochemical studies may provide more risk factors that are involved in causing IMDs. Frequent update and accurate reviewing are required for deeper insight of a disease.

Conflicts of Interest There is no conflict between the authors.

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Chapter 5
Impaired Lipid Metabolism in Metabolic Disorders

Kamran Haider, Kanwal Rehman, and Muhammad Sajid Hamid Akash

Abstract Metabolic disorders relating to impaired lipid metabolism have become an annoying issue in current era. Energy dense diet coupled with sedentary life-style are crucial triggering events for these metabolic disorders that significantly disturb various metabolic pathways notably carbohydrate and lipid homeostasis. The ultimately developed metabolic syndromes such as lactic acidosis, obesity, non-alcoholic fatty liver disease, type 2 diabetes, polycystic ovaries, and neurodegenerative disorders are potential health risks that disturb the quality of life. Deposition of lipids in the non-adipose tissues such as muscle and liver is also strongly interlinked with insulin resistance. Ultimately, loss of particular function and differentiation of β-cells is caused by progressive fat deposition in the pancreas leading to reduction in insulin secretion. So, strategies to prevent, compete, and overcome these metabolic disturbances are radical therapeutic and nutritional interventions, mainly involving life-style management and weight reduction. The ultimate approaches anticipate defensive role in abating or minimizing these undesirable consequences and improve quality of life.

Keywords Bioactive lipids · Insulin resistance · Metabolic syndrome · Lipid homeostasis

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Introduction

Metabolic syndrome is a complex condition combined in a sole entity as a set of metabolic abnormalities that possesses similarities in relationship with ectopic lipid accumulation, chronic low-grade inflammation, and insulin resistance [1]. Instead, the increased prevalence of obesity along with sedentary habits, are crucial risk factors for sequential progress of metabolic syndromes worldwide [2]. As lipids are the mandatory elements of almost all cells, they play healthy role in energy production, as a structural component and in signaling process. Irrespective of their notable functions, their excessive availability and ultimate abnormal intracellular accumulation subsequently provokes numerous metabolic disorders [3]. Among these, lactic acidosis is an alarming as well as life-threatening condition that is associated with poor outcomes and mortality [4]. Metabolic acidosis is now frequently observed especially among patients undergoing intensive care or emergency treatment. Even acute acidosis perhaps leads to many diseases and may consequently end in total organ failure [5]. Similarly, overweight and obesity also contribute to high risk factors for incidence and progression of metabolic syndromes in recent years and now becoming a global health problem [6]. Evidently, obesity is strongly interlinked with other potential metabolic comorbidities like cardiovascular problems, diabetes, and non-alcoholic fatty liver disease (NAFLD) [7].

Likewise, non-alcoholic fatty liver disease coupled with metabolic syndrome also constitutes high prevalence. So, better lifestyle adaptation together with physical exercise remains the best strategies to compete them [8]. In the same way, diabetes mellitus is among the most prevalent chronic metabolic disease which is characterized by persistently elevated blood glucose level. Its prevalence among adults in 2010 was 6.4% and expected to increase up to 7.7% by 2030 [9]. Moreover, polycystic ovary syndrome (PCOS) have also impregnable relationship with the metabolic disturbance and now becoming principal causative factor for female infertility [10]. Like the treatments of other metabolic syndromes, healthy diet parallel with medication that improve insulin sensitivity, are the better therapeutic options for abating the infuriating factors of PCOS [11]. In addition, recent studies have also reported the contribution of lipids as well as lipid transporters in number of age-related neurodegenerative diseases owing neuroinflammation [12]. Some of the important metabolic disorders are discussed in this chapter.

Lactic Acidosis

Energy in the form of ATP is the crucial requirement for all tissues to perform their assigned functions. Like humans, this happens by transformation of energy rich molecule (glucose) to end product (CO_2). This occurs either by aerobic or anaerobic process [13]. In anaerobic respiration, especially due to short supply of oxygen, lactate is formed which starts accumulating in the body [13]. Initially, this lactate

was just considered as a waste product as a consequence of anaerobic respiration. But recently, its metabolism is significantly studied which demonstrates its significance in many physiological and pathological conditions [14]. Lactic acid has also an influential role in energy regulations, such as cardiac myocytes utilize lactate as a fuel, contributing 10–15% of energy provision at rest. In addition to energy supply to cardiac myocytes, a study in rodents exhibits impaired myocardial function upon lactate deprivation from circulation. Similar effects were also prominent in brain as well as in kidney [15]. Alternatively, hyperlactatemia is engaged with several pathological conditions, such as various cardiac complications like cardiac arrest, acute coronary syndrome, and cardiogenic shock, where lactate clearance is associated with more reliable and better outcomes [16]. Also, lactate is elevated in injured brain, making association with traumatic brain injury [17]. Likewise, it also potentiates ischemic brain injury by activation of GPR81-mediated signaling, providing a target for treating ischemic brain injury by blocking GPR81 receptors. Also, presence of GPR81 receptors in many intracellular organelles demonstrates its multiple functions and associated complications [15].

Lactate being vital energy source as well as substantial metabolic substrates, also activates GPR81 receptor, so it manipulates its role in averting lipolysis in adipose tissues. This also paved a novel pathway for treating dyslipidemia along with other metabolic disorders [18]. Furthermore, lactic acid bacteria are also proved as considerable tool for targeting fat related metabolic disorders. Such as, oral administration of lactic acid bacteria (*Lactobacillus gasseri* NH) diminishes fatty acid synthesis and so, able to protect the body from number of metabolic disorders which are the consequences of impaired lipid metabolism [19].

Obesity

According to World Health Organization (WHO), obesity is an increased or abnormal fat accumulation in the body associated with certain risks for health. Mostly body mass index (BMI) greater than 25 kg/m^2 is regarded as overweight, while BMI greater than 30 kg/m^2 is considered as obese (obesity). And alarmingly, this is becoming a global problem [20]. Its prevalence has been raising worldwide and reached up to pandemic level in about previous 50 years. The potential trembling problem is the associated health risks with it, such as myocardial infraction, fatty liver disease, osteoarthritis, hypertension, type 2 diabetes, stroke, and sleep apnea, all leading towards disturbance in quality of life as well as life expectancy [21]. Actually, the fundamental triggering events associated with such a metabolic disorder and now becoming the major global health issues are the luxurious lifestyle and improper diet. Combined effect of environmental factors and genetic makeup along with irregular energy balance, further augmented by improper diet consequently provoke obesity [22].

Sleep deprivation is considered as one of the causative factors for obesity. The unique mechanism linking sleep deprivation and obesity is still debatable. However,

certain possible association has been developed. Such as, lack of sleep is associated with chronic activation of sympathetic nervous system, and direct sympathetic innervations to adipose tissues promotes stimulation of lipolysis, giving rise to elevated free fatty acids [23]. Additionally, studies have also indicated that chronic stress and sleep deprivation are responsible for initiation and progression of metabolic disorders involving obesity. This mechanism is related to the alteration in neuroendocrine response and hyperactivation of hypothalamic-pituitary-adrenal axis [24]. Admittedly, sleep loss is associated with low leptin and increased ghrelin, leading towards more hunger and ultimately obesity [25]. Meanwhile, in vitro studies have also indicated that hypoxia mainly obstructs lipoprotein lipase activity in differentiated individually preadipocytes. Yet, in vivo studies demonstrate elevated postprandial non-esterified fatty acids (NEFA), during small sessions involving intermitted hypoxia [26]. It is obvious that improving sleep hobbits via sleep as well as treating sleep disorders along with other radical nutritional interventions can be best therapeutic approach in prophylaxis of metabolic disorders [24].

Non-Alcoholic Fatty Liver Disease

NAFLD signifies the presence of macrovascular alteration in the absence of considerable alcoholic use without any inflammation (stenosis) and lobular inflammation. It is categorized into two subgroups; one is non-alcoholic fatty liver (NAFL) and other is non-alcoholic steatohepatitis (NASH). Likewise, NASH is defined with existence of hepatic steatosis as well as inflammation along with hepatic injury [27]. While on the other hand, NAFLD is defined with liver manifestation, accompanied by radiographic and histologic evidence for the presence of fat deposition in liver, may or may not be linked with inflammation [28].

NAFLD is generally affiliated with metabolic syndrome, hyperlipidemia, diabetes, and obesity. Generally, approximately 80% of patients having metabolic syndromes also possess NAFLD [27]. Unlike most other disorders, NAFLD do not follow sequenced/organized progression, means a person may be prone to fibrosis without developing NASH stage, or may be exposed to liver cancer without having fibrosis or histologic NASH [29]. In fact, the main disturbance in lipid metabolism during NAFLD is due to elevated de novo lipogenesis and hepatic uptake, which is accompanied with insufficient rise in compensatory fatty acid oxidation (Fig. 5.1). This give rise to increase in cellular damage and further aids disease progression by triggering oxidative stress, particularly with the raised oxidation in cytochromes and also in peroxisomes, along with mitochondrial dysfunction [30]. Alternatively, the exact molecular mechanism concerned with fat deposition in liver is not completely understood. Yet, compromised mitochondrial function, adipose tissue inflammation, lipotoxicity, oxidative stress, insulin resistance, and endoplasmic reticulum stress play a critical role [31]. Actually, during normal physiological process, substrate supply and oxidation including secretion tightly control the lipid

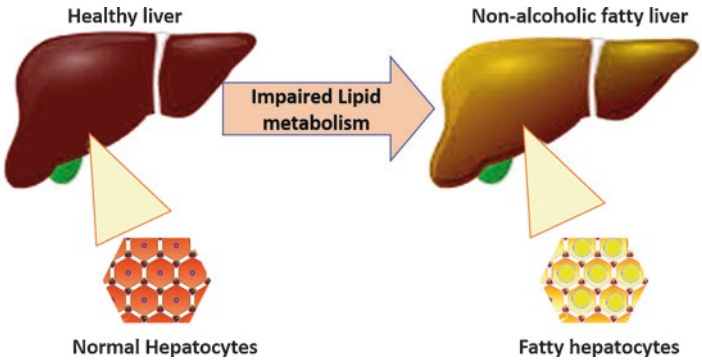

Fig. 5.1 *Comparison of healthy liver and non-alcoholic fatty liver*: Both macroscopic and microscopic view of healthy and non-alcoholic fatty liver demonstrates clear difference. Presence of fat in non-alcoholic fatty liver is seen easily, both macroscopically as well as microscopically

homeostasis. But other toxins also specifically mediates its toxic effect and arouses switching to chronic fatty liver disease [32].

Besides ethanol, epidemiological studies have illustrated that consumption of dietary cholesterol elicits strong association with development of fatty liver disease. Moreover, consumption of high fat diet along with alcohol has more detrimental effect and induces liver injury, in contrast to simple high-fat diet without cholesterol and alcohol [33]. Meanwhile, several mechanisms give rise to steatosis such as (i) increased fat diet and enhanced adipose lipolysis, (ii) diminished fat export in VLDL-TG form, (iii) downregulation in free fatty β-oxidation, and (iv) elevated de novo lipogenesis. So, subsequently developed hepatic steatosis is helpful for histological identification of NAFLD [31].

Importantly, treatment strategies to overcome and overt NAFLD include healthy life-style adaptation and nutritional interventions. Lifestyle management especially dietary restriction along with regular physical exercise can reverse NAFLD, as weight reduction has dose-response relationship with treating NAFLD. Particularly, weight reduction $\geq$10% is interlinked with improvement in almost half of patients having liver fibrosis [34]. No doubt, weight reduction is laborious to attain and then maintain. For this, NAFLD patients necessitate also pharmacotherapy [35]. Therefore, a number of novel targets are under consideration in randomized clinical trials to prevent the consequence of disease from last 5–10 years [34]. Recently, one study has indicated that protease-activated receptors 2 (PAR2) contributes a role in lipid homeostasis and cholesterol in NAFLD. It is demonstrated that PAR2 mediates its role in suppressing reverse cholesterol transport and also in lipid breakdown. An evidence from a study on mice presents reduction in cholesterol synthesis and increased β-oxidation by PAR2 deficiency. Thus, PAR2 can be a novel target in treating NAFLD and other associated metabolic conditions [36]. Among currently available drugs, pioglitazone and vitamin E have shown positive outcomes. Additionally, a single-center study has also demonstrated that vitamin E may have

preventive/prophylactic effect on liver decompensation. In addition to this, five drugs have been entered in phase 3 development for treating NASH [34].

Type 2 Diabetes Mellitus

Among other metabolic disorders involving lipid-impaired metabolism, diabetes is the most prevalent metabolic disorder that ultimately leads towards disruption in metabolic pathways. Currently, T2DM has become a global health problem, with the prevalence of 8.8% and its incidence is promptly increasing. The major consequence of T2DM is production of hazardous metabolites that consequently leads towards total organ failure [37, 38]. Insulin resistance, which is a major triggering factor possesses strong association with T2D and also linked with other metabolic disorders such as hypertension, hyperglycemia, and obesity [39, 40].

Although the exact underlying molecular mechanism responsible for insulin resistance is still unclear, many studies have dictated strong association between abnormal lipid metabolism and insulin resistance [41]. Also, deposition of bioactive lipids in the non-adipose tissues such as muscle and liver is also strongly interlinked with insulin resistance [3]. Ultimately, loss of particular function and dedifferentiation of β-cells are caused by progressive fat deposition in the pancreas (Fig. 5.2). Subsequently, elevated fat removal from the pancreas and liver reverses the hyperglycemia to normal levels, which can be accomplished by reduction in body weight [42]. Actually, too much supply of calorie dense foods and subsequent diminished physical activity facilitate the environment that favors increased lipid accumulation. Other than this, there are also several factors on cellular levels that promote lipid deposition in these non-adipose tissues, which cause disturbance in metabolism and function of adipose tissues [3].

For this reason, calorie restriction can be a better therapeutic strategy and nutritional intervention. One study has indicated that calorie restriction meliorates insulin sensitivity and also lipid metabolism in gestational diabetes mellitus offspring

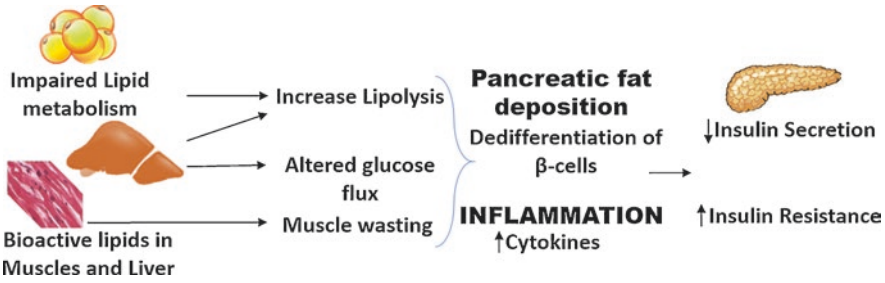

Fig. 5.2 *Comparison of healthy and diabetic pancreas*: Diabetic pancreas give rise to insufficient and functionally compromised insulin production. This ultimately results in elevated glucose level in general circulation, which is clearly demonstrated in this figure

mainly by elevation in AKT phosphorylation and reduction in PTEN activation in liver [42]. Whereas, an abnormality in mitochondrial function that leads towards incomplete fatty acid oxidation is also a potential contributor in insulin resistance and associated T2DM [43]. Truly, this abnormality in mitochondrial function also provokes intracellular accumulation of diacylglycerol (DAG), an active lipid associated with downregulation of insulin signaling pathway and so, accordingly potentiates insulin resistance [44]. Several studies have also elucidated that abnormal elevation of DAG is associated with Protein Kinase C activation, which subsequently disturbs the normal insulin stimulated signaling, and ultimately giving rise to insulin resistance and afterward T2DM [45]. Correspondingly, augmenting sphingolipids in non-adipose tissues is potential mediator of insulin resistance and also establishes strong association with cardiac failure, diabetes, hypertension, and atherosclerosis [46].

Evidently, the therapeutic approach to prevent and obviating this metabolic disorder is diet mainly composed of vegetables and fruits along with minimum use of saturated fat. Dietary Guidelines for Americans recommended that adaptation to dietary guidelines lowers the circulating ceramide level, which ultimately ends up in improving insulin sensitivity [47]. So, disturbance in lipid metabolism has contribution in incidence and progression of insulin resistance and T2DM.

Polycystic Ovary Syndrome

PCOS is a complicated metabolic syndrome, primarily associated with hyperandrogenism as well as chronic anovulation, with the prevalence of 6–10% in women of reproductive age [48]. Generally linked with multiple pathophysiology such as endocrine, genetics, environmental, and metabolic factors. Women victimized by PCOS have to face many complications along with many metabolic derangements like hypertension, obesity, dyslipidemia, and insulin resistance. Such women are also more vulnerable to early onset of cardiovascular complications [49]. Accordingly, women with PCOS possess higher abdominal adiposity as compared to normal women having comparable BMI. Likewise, this phenotypic expression of adiposity may start in adolescence. Furthermore, elevated subcutaneous adiposity may start in adolescence. Additionally, elevated subcutaneous abdominal adiposity in PCOS women dictates diminished ability of adipose tissues for safely storing fat [50].

The chief manifestation of PCOS is diluted ovulation, particularly interlinked with obesity or other lipid metabolic disorders. The prevalence of obese women with PCOS is nearly 50–80%. Actually, obesity has association with irregular adipokine secretion, combined with increased free fatty acids that finally end up in insulin resistance. Generally, 20% of obese women having PCOS demonstrated abnormal glucose tolerance [51]. Despite the exact pathogenesis of PCOS is unclear, a number of mechanisms has been proposed and still debatable. Insulin resistance and subsequent hyperinsulinemia and atherogenic dyslipidemia are central to the

pathogenesis of PCOS. Further, obesity and hypertension exacerbate the underlying metabolic syndrome. Additionally, PCOS is further involved in the pathogenesis of cancer, obstructive sleep apnea, diabetes, and psychological problems like depression [52].

Alternatively, the primary symptoms associated with PCOS are dermatological signs (alopecia, hirsutism, and acne) along with the abnormal menses. In addition to these, biochemical alterations linked with elevated testosterone level and increased pituitary LH release are the consequences of insulin resistance and subsequent hyperinsulinemia. Likewise, hyperandrogenism in conjugation with elevated LH level leads to disturbance in physiological process related to ovarian follicular maturation and finally gives to anovulatory cycles [48]. In fact, dyslipidemia is considered to play a key role in the incidence and prevalence of PCOS. Thus, lipid abnormalities are accompanied by increased low-density lipoprotein (VLDL) and triglycerides (TGs), while diminished high density lipoproteins (HDL) are often seen in women with PCOS. Subsequently, such women have increased waist to hip ratio [53]. In addition to this, one pilot study has also demonstrated that women having PCOS exhibits reduced capability of switching during the overnight fasting along with daily metabolism from glucose to lipid oxidation [50]. It is known that polyunsaturated fatty acids (PUFAs) and their ultimate derivatives have fundamental contribution in the dissemination of PCOS. This is evident from abnormal level of FFAs, PUFAs metabolites, and phosphatidylcholine in women with PCOS [51].

Finally discussing all the pathogenesis and ultimate consequences of PCOS, there is a fundamental need for the pharmacological and non-pharmacological interventions for tackling PCOS. Non-pharmacological interventions include life-style management such as weight reduction, maintaining BMI which diminishes insulin resistance and subsequently improves insulin sensitivity, leading towards protective effect on metabolic and reproductive features. Additionally, proper counseling and nutritional supplements like inositol and N-acetylcysteine has also shown beneficial outcomes [54]. Coming towards pharmacological treatments, drugs that improve lipid profile are better therapeutic targets for PCOS. Such as metformin reduces body weight, FSH and glucose levels as well as androgen. It is utilized for the treatment of PCOS [11]. So, we can summarize that strategies must be adopted for subsiding or mitigating the incidence and progression of PCOS and its ultimate consequences.

Impaired Lipid Metabolism and Neuroinflammation

As brain development is a sequenced process usually accomplished by the unique/particular well-defined stages regarding growth and maturation. Among these, one of the pivotal events is formation of myelin sheath. Dietary lipids have an influential role in this process [55]. Recently, a study in male rats interprets that high fat diet ingestion for nine weeks induces obesity and also affects incidence and dissemination of neuroinflammation. This neuroinflammatory response was

generated in both amygdaloid and hypothalamic nuclei [56]. In fact, high fat diet for a single day boosts expression of TNF-α and IL-6 along with stimulation of microglial cells in rodents. Further, 3 days exposure of high fat diet raised gliosis augmented by inflammation, and promotes marker of neuronal injury [57]. The ultimate neuroinflammation has a detrimental effect and potential hallmark for a number of neuropsychiatric disorders like bi-polar disorders, depression, and schizophrenia. Correspondingly, elevated levels of inflammatory biomarkers like chemokines and cytokines in psychiatric patients clearly indicate association of inflammation and psychiatric disorders [58].

Dietary interventions including long chain-polyunsaturated fatty acids (LC-PUFA) are considered to manipulate a advantageous role in neuroinflammation and prohibits undesirable outcomes. As LC-PUFAs, significantly of n-3 family elicits anti-inflammatory and pro-resolution characteristics. Additionally, LC-PUFAs imparts their beneficial role by synthesis of specialized pro-resolution mediators (SPMs). These SPMs then reverses inflammation, thus possessing defensive and neuroprotective effects and mitigates neuroinflammation [59]. Additionally, another bioactive lipid oleoylethanolamide (OEA) also offers favorable profile for alcohol abuse. Several preclinical studies have demonstrated that OEA possesses anti-inflammatory and anti-oxidant properties, thus manipulating a neuroprotective effect in alcohol abusers. Also, endogenous and exogenous OEA have averting action on proinflammatory chemokines and cytokines and thus, impart protective effect against neuroinflammation [60].

Summary and Future Prospective

These convincingly aforementioned evidence dictates that metabolic disorders particularly owing to lipid-impaired metabolism are relatively complicated health problems. Accordingly, the associated health risks like lactic acidosis, hypertension, cardiovascular complications, obesity, diabetes, fatty livers, polycystic ovaries along with neurodegenerative disorders are increasing promptly in recent days. Actually, genetic factors along with environmental factors like energy dense diet, physical inactivity, and sedentary life-style are potential triggering events for provoking and dissemination of metabolic disorders. It necessitates the utmost need of pharmacological along with non-pharmacological strategies like nutritional interventions and better life-style management for safeguarding the undesirable complications engaged with metabolic disorders. Calorie restricted diet having no or minimum saturated fatty acids along with regular physical exercise and better life-adaptations are palliative strategies to minimize metabolic disorders and protects from future consequences.

Conflict of Interest Nothing to declare.

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Chapter 6
Impaired Thyroid Function in Metabolic Disorders

Yusra Habib Khan, Amna Saifullah, Tauqeer Hussain Mallhi, Allah Bukhsh, and Tahir Mehmood Khan

Abstract The tri-iodothyronine (T3) and thyroxine (T4) are the two important thyroid hormones through which endocrine system controls the cellular and intracellular functions of body. In response to certain stimuli, the hypothalamic thyrotropin-releasing hormone (TRH) governs the release of thyroid stimulating hormone (TSH) from anterior pituitary. The thyroid hormones are synthesised by the action of TSH on membrane receptors of thyroid cell follicle and regulated by negative feedback effect of circulating T3 and T4 on anterior pituitary. Thyroid hormones play their important role in growth, development and regulation of metabolism in body. Alterations in normal regulation mechanisms of body in certain metabolic disorders result in impaired thyroid function. Diminished thyroid activity due to decreased production of thyroid hormones or tissue resistance is termed as hypothyroidism. While hyperthyroidism is characterised by overactive thyroid glands leading to increased production and secretion of thyroid hormones. Which may result in a subsequent increase in metabolic rate of body. On the other hand, impaired thyroid function may also result in metabolic abnormalities. Increased

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level of leptin hormones in obesity results in increased secretion of TRH and TSH and ultimate increase in fT3. Hyperthyroidism results in increased intestinal glucose absorption, hyperglycemia, elevated hepatic glucose turnover, raised levels of fasting and postprandial insulin and pro-insulin leading to hyperinsulinemia and marked rise in free fatty acid concentrations. While hypothyroidism is associated with decreased intestinal absorption, decreased hepatic output and decreased peripheral utilization of glucose. However, poor glycaemic control in diabetic patients impairs the conversion of T3 to T4, decreases the TSH level and response to TRH, and ultimate thyroid enlargement and development of thyroid nodules. In hypothyroid patients, an increase in total cholesterol and LDL concentration, a decrease in catabolism of LDL, decreased activity of LPL and ultimate decrease in clearance of triglycerides rich lipoproteins are observed. An increase in activity of catabolic pathways in hyperthyroid patients may lead to enhanced synthesis and degradation of lipids, and hypertriglyceridemia. Hyperthyroidism may stimulate osteoclasts formation resulting in reduced bone mineral density and increased risk of fractures. However, the underlying mechanism involved in detrimental effects of hypothyroidism on bone mineral density is still not clear.

Introduction to Thyroid Hormones (TH)

The nervous system controls the cellular and intracellular functions of body through endocrine system. The thyroid gland is a major component of endocrine system and regulates the metabolism of cells and tissues by producing thyroid hormones. The two most important thyroid hormones are tri-iodothyronine (T3) and thyroxine (T4) [1–3].

Biosynthesis of Thyroid Hormones

In response to certain stimuli, the hypothalamic thyrotropin-releasing hormone (TRH) governs the release of thyroid stimulating hormone (TSH) from anterior pituitary. The action of TSH on membrane receptors of thyroid cell follicle results in the synthesis of thyroid hormones. This process is mediated by activation of cAMP (cyclic adenosine monophosphate) and phosphatidyl inositol 3-kinases (PI3Ks). Following steps are involved in the synthesis, storage and secretion of thyroid hormones.

- Plasma iodide uptake by thyroid follicle cells
- Organification of iodide (Oxidation of iodide and incorporation in thyroglobulin)
- Iodination of tyrosine residues
- Secretion of thyroid hormones through endocytotic vesicles

The plasma iodide ions are transported to the lumen of thyrocytes with the help of two transporters: Na^+/I^- symporters (NIS) located at basolateral surface and an I^-/Cl^- transporter located at apical membranes of thyrocytes. An enzyme named as thyro-peroxidase catalyses the oxidation of iodide ions into elementary iodine and incorporation of oxidised ions to thyroglobulin (a glycoprotein, synthesized in thyroid glands). Hydrogen peroxide (H_2O_2) acts as an oxidising agent in this process. The iodination of tyrosine residues of thyroglobulin results in the formation of mono-iodotyrosine (MIT) and di-iodotyrosine (DIT). The coupling of MIT and DIT results in formation of T3 and the T4 is produced by the coupling of two DIT molecules (Fig. 6.1) [1, 2, 4].

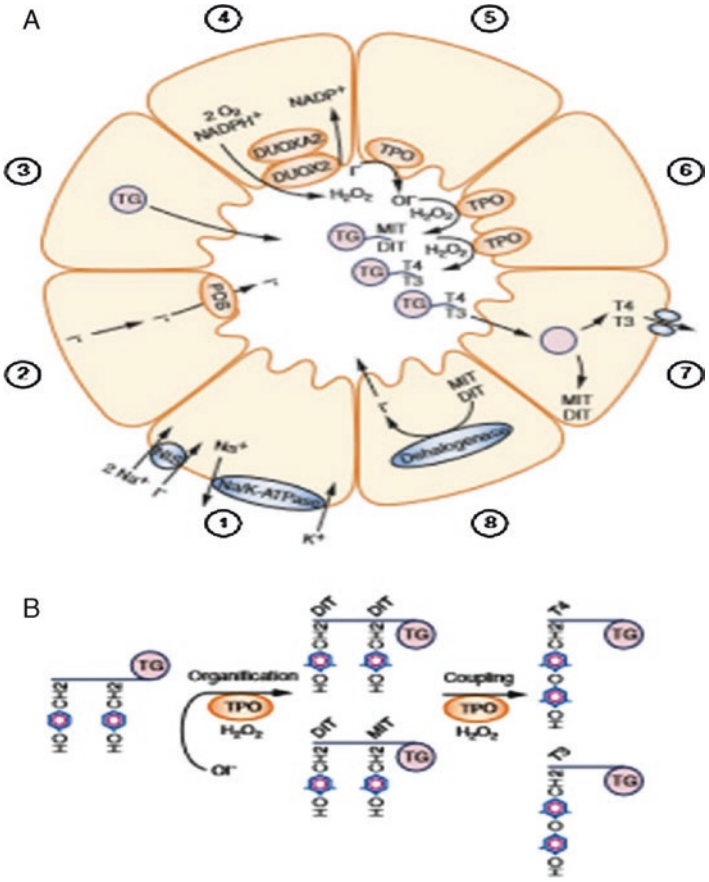

Fig. 6.1 Biosynthesis of thyroid hormones. (**a**) Key steps involved in biosynthesis of thyroid hormones, 1: uptake of iodide ions by Na+/I- symporters (NIS), 2: transport of iodine to follicular lumen, 3: secretion of thyroglobulin (TG), 4: generation of hydrogen peroxide (H2O2), 5: oxidation of iodine, 6: organification/iodination of tyrosine residues, 7: internalisation of iodide TG, 8: deiodination and release of iodine for recycling of hormone. (**b**) Organification and coupling reactions. (Permission is granted by Elsevier under the license number: 4704471193943) [4]

Secretion of Thyroid Hormones

In response to negative feedback mechanism, the thyroglobulin molecule is taken up by the endocytotic vesicles of thyrocytes. Upon fusion of endocytotic vesicles with lysosomes, T3 and T4 are liberated in plasma by enzymatic proteolysis of thyroglobulin. The T3 is more active form of thyroid hormones but it is present in small quantities in human body [1, 5].

Regulation of Thyroid Hormones

The synthesis of thyroid hormones is regulated by negative feedback effect of circulating T3 and T4 on anterior pituitary. Low blood levels of thyroid hormones trigger the release of TRH and TSH, while high levels of these hormones cause a 'shut down' to the release of TRH and TSH. Plasma iodide concentration is also an important factor in regulation of thyroid hormones. An increased iodine intake with increased plasma iodide concentration will result in increased hormone production and decreased TSH secretion and vice versa [1, 2].

Transport, Metabolism and Excretion of Thyroid Hormones

The thyroid hormones bind with three plasma proteins: a α-globulin named as thyroxine-binding globulin (TBG), transthyretin formerly known as thyroid binding pre-albumin (TTR) and albu-min. The variations in concentration of TBG are more important than other binding proteins, as thyroid hormones have greater affinity for TBG [6]. The liver is major metabolising site for thyroid hormones where they undergo de-iodination, decarboxylation, deamination, glucuronidation and sulfation. The metabolised products are excreted primarily in bile and partly in urine [1, 2].

Functions of Thyroid Hormones

Thyroid hormones are primarily involved in growth, development and regulation of metabolism including basal metabolic rate, carbohydrates/lipid metabolism, thermogenesis and oxygen consumption [1–3, 7, 8].

Impaired Thyroid Functions

Thyroid anomalies are among the most common endocrine disorders and subclinical thyroid disease in middle-aged and elderly is quite prevalent.

Hypothyroidism

Decreased production of thyroid hormones or tissue resistance leads to diminished thyroid activity termed as hypothyroidism. It is manifested majorly by a reversible slowing of all bodily functions [1]. There are three types of hypothyroidism: primary, secondary and tertiary hypothyroidism (also known as central hypothyroidism). Primary hypothyroidism is characterised by low level of thyroid hormones primarily caused by destruction of thyroid glands [9]. It accounts for more than 95% of adult cases. Central hypothyroidism is caused by insufficient stimulation of thyroid glands secondary to hypothalamic or pituitary disorders and is associated with decreased levels of T3, T4 and normal or low levels of TSH. Patients with central hypothyroidism have either a failure of the anterior pituitary to secrete TSH (also known as secondary hypothyroidism), failure of the hypothalamus to secrete thyroid releasing hormone (TRH) known as tertiary hypothyroidism, or, in some rare cases, a TSH deficiency with no other findings of pituitary or hypothalamus abnormality. The most common cause of central hypothyroidism is pituitary mass lesions. Treatment, such as surgery or radiation therapy for these lesions, can also lead to central hypothyroidism [10].

Clinical Manifestations of Hypothyroidism

Slow metabolic rate, slow speech, deep hoarse voice, sensitivity to cold, dry skin, bradycardia, mental impairment, hypercholesterolemia, lethargy and myxoedema (subcutaneous deposition of glycosaminoglycan's induced characteristic thickening of skin along with hypothyroidism) are common signs and symptoms of hypothyroidism. Patients presented with these signs and symptoms along with increased TSH and decreased T4 and/or T3 levels are diagnosed with clinical (overt) hypothyroidism. However, biochemical findings of serum TSH levels above and serum T4 and/or T3 levels within the reference range indicate subclinical hypothyroidism [9, 11].

Aetiology of Hypothyroidism

The most common causes of hypothyroidism are autoimmune destruction of thyroid glands (Hashimoto's thyroiditis), radiation, thyroidectomy, iodine deficiency and drugs. The congenital hypothyroidism is most common endocrine disorder among infants (1 in every 3000–4000) caused by deficiency of thyroid hormones during foetal development. It leads to growth and mental retardation among children [3].

Hyperthyroidism or Thyrotoxicosis

Hyperthyroidism is characterised by increased thyroid hormone synthesis and secretion from the thyroid gland, whereas thyrotoxicosis refers to the clinical syndrome of excess circulating thyroid hormones, irrespective of the source [3].

Clinical Manifestations of Thyrotoxicosis

Increased metabolic rate, intolerance to heat along with increase in skin temperature and sweating, hair loss/thinning, increased appetite but weight loss, increased thirst, diarrhoea, nervousness, tremors, tachycardia, psychosis, osteoporosis and cardiovascular abnormalities are common manifestations of thyrotoxicosis [3].

Aetiology of Thyrotoxicosis

Thyrotoxicosis is classified in certain types but two types are commonly used in the literature, i.e. Grave's disease (diffuse toxic goitre) and toxic nodular goitre [3].

Grave's Disease

It is an autoimmune condition caused by the abnormal production of IgG immunoglobin (also known as thyroid receptor antibodies TRABs). IgG mimics the action of TSH at its receptors by causing the increased activation of receptors and ultimately an augmented secretion of TH. Maternal TRABs can cross placenta resulting in transient neonatal thyrotoxicosis [1, 3].

Toxic Nodular Goitre

It is common in elder females presented with nodular goitre. T3/FT3 (FT3: Free T3) is strikingly elevated and FT4 (FT4: free T4) becomes normal/moderately elevated in this condition [1, 3].

Other Thyroid Disorders

Simple Non-Toxic Goitre

Simple non-toxic goitre is a condition associated with prolonged dietary deficiency of iodine causing elevation in the plasma level of TRH. This may eventually leads to enlargement of thyroid glands with normal levels of thyroid hormones except in severe iodine deficiencies [2].

Sub-Acute Thyroiditis

It is associated with increased secretion of stored thyroid hormones as a consequence of viral infection of thyroid glands, also known as spontaneously resolving thyrotoxicosis [2].

Thyroid Neoplasms

Thyroid neoplasm is a neoplasm or tumour of the thyroid. It can be a benign tumour such as thyroid adenoma, or it can be a malignant neoplasm (thyroid cancer), such as papillary, follicular, medullary or anaplastic thyroid cancer [2].

Metabolic Abnormalities and Thyroid Functions

Alterations in normal regulation mechanisms of body in certain metabolic disorders result in impaired thyroid function. On the other hand, thyroid dysfunction may interfere with normal metabolic processes of the body, leading to metabolic abnormalities. In this chapter, we will discuss both the causes and consequences of impaired thyroid functions in relation to metabolic disorders.

Thyroid Hormones and Obesity

A bidirectional association exists between obesity and thyroid hormones, with influence of obesity on thyroid function and hypothyroidism affecting body mass index (BMI) and body weight. The anomalies of thyroid functions are frequently observed in obese individuals [12].

The leptin is a 16 kilo-dalton hormone released from adipose tissues and acts on arcuate neurons of hypothalamus. The role of leptin signalling on the maintenance of hypothalamic TRH expression has recently been reported. The leptin hormone controls the thyroid function via acting directly on leptin receptors present in TRH neurons, or through projections of arcuate neuron in TRH neurons. Increased level of adipocytes in obese individuals results in increased release of leptin which consequently stimulates the secretion of TRH and TSH via JAK-2/STAT-3 pathway, leading to hypothyroidism (Fig. 6.2) [13].

A positive correlation has been observed between body mass index, body weight and thyrotropin (TSH) in obese individuals although thyroid function seems to be normal [14]. Many studies in different age groups have shown an elevation in the level of TSH in obesity. Slight elevations in the serum TSH level along with normal thyroid functions among obese subjects can be characterised as subclinical hyperthyroidism. Among the causes of increased TSH levels in obesity, iodine

deficiency or autoimmune thyroiditis induced subclinical hypothyroidism, leptin derived disturbance in hypothalamic-pituitary functions, partially disturbed negative feedback mechanism due to partial bio-inactivation of TSH proteins in obese individuals, hormone resistance owing to increased TSH levels in obesity, increase in TSH levels as a consequence of adaptation to increased resting energy expenditure (REE) to cope up with increased energy expenditure are postulated to be important ones [15].

It has been reported that increased TSH level may not necessarily increase total and free T4 levels in obese subjects. However, several studies have suggested a moderate increase in the level of free and total T3 in obese individuals. Change in

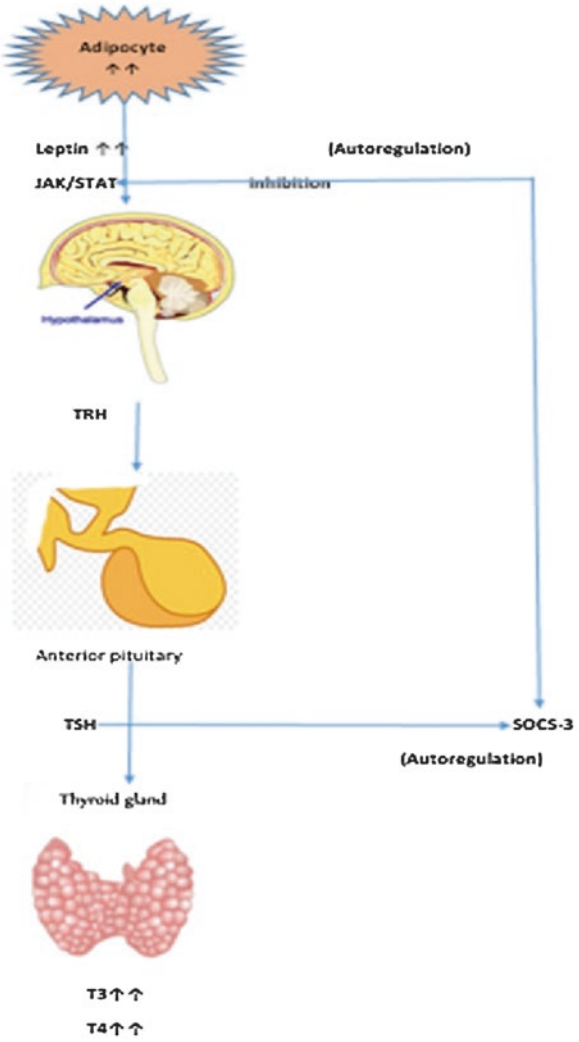

Fig. 6.2 Release of leptin under the influence of adipocytes. The leptin released as a result of expanding adipocytes causes the secretion of thyrotropin-releasing hormone (TRH) and thyrotropin (TSH), via its action on Janus activating kinase (JAK)-2/signal transducer and activator of transcription (STAT)-3 factor, which in turn sustains the secretion of leptin. The circulating leptin also stimulates the suppressor of cytokine signaling-3 (SOCS-3), with ultimate inhibition of leptin signalling (auto-regulation) T4, thyroxine; T3, tri-iodothyronine

monodeiodination pathways (conversion of T4 to T3) during obesity leads to increased levels of FT3 among obese subjects. Production of T3 is increased with decreased production of rT3 (reverse T3) in obesity compared to equal production of both rT3 and T3 in normal weight individuals [15]. Available data conclude elevated thyroid levels as a consequence rather than a cause of obesity.

Elevated levels of TSH in obese individuals cause the decreased expression of TSH receptors and ultimate down regulation of TH receptors and actions. As a consequence, the levels of serum TSH and fT3 are further increased in obesity [16]. Hence, it is concluded that TSH secretion is impaired in obesity [17].

Thyroid Hormones and Diabetes Mellitus

Since autoimmune thyroiditis is an important aetiological factor in both hyper- and hypothyroidism. It is not unusual to find concomitant autoimmune thyroid dysfunction (AITD) and type 1 diabetes (which is also autoimmune in nature) with prevalence of AITD in almost 17–30% of type 1 diabetics [18]. The risk of involvement of genetic factors in the co-occurrence of both diseases can never be ruled out. Among the susceptibility factors of concurrence of thyroid disorders and diabetes type 1, mutations in major histocompatibility complex (MHC) locus on chromosome 6p21, protein tyrosine phosphatase, non-receptor type 22 (PTPN22), which encodes lymphoid tyrosine phosphatase, a negative regulator of T-cell antigen receptor (CD3: CD3 (cluster of differentiation 3)) signalling and the cytotoxic T-lymphocyte antigen-4 (CTlA4) gene have both been confirmed as major joint susceptibility genes for type 1 diabetes and AITD. The prevalence of impaired thyroid functioning is highest in patients with type 1 diabetes [19].

Thyroid Hormones Regulation of Glucose Homeostasis

Thyroid hormones regulate glucose balance in body in different ways: regulation of glucose homeostasis, modification of circulating insulin levels and counter regulatory hormones, intestinal absorption of glucose, hepatic production of glucose and uptake of glucose by peripheral tissues [20]. Thyroid hormone maintains glucose homeostasis by working with two opposite mechanism; insulin antagonism and insulin synergism. These hormones act differently at different action sites of insulin such as adipose tissues, liver and skeletal muscles.

1. Insulin antagonism (liver): TH produces insulin antagonistic effects by increasing the hepatic gluconeogenesis and glycogenolysis as well as by increasing the intestinal absorption of glucose. The T3 is believed to increase the expression of glucose-6 phosphatase which facilitates gluconeogenesis and glycogenolysis by hydrolysis of glucose 6 phosphate. Thyroid hormones also influence other enzymes involved in hepatic gluconeogenesis such as phosphoenol pyruvate

carboxy kinase (PEPCK), the enzyme that catalyses the rate-limiting step of glucose production and pyruvate carboxylase, an enzyme involved in the bioconversion of pyruvate to oxaloacetate. Thyroid hormones also decrease the hepatic glyconeogenesis by decreasing the expression of Akt 2, a serine/threonine protein kinase, involved in glycogen synthesis (Fig. 6.3) [21].

2. Insulin synergism (peripheral tissues): TH produces synergistic effects by increasing the glycolysis and transport of glucose via up-regulated expression of phosphoglycerate kinase (PGK) and insulin regulated glucose transporter type 4 (GLUT 4) found in myocytes and adipocytes, respectively. This increases the basal and insulin stimulated glucose utilisation in peripheral tissues (Fig. 6.3) [21].

Hyperthyroidism and Diabetes

Elevations of thyroid hormones lead to increased hepatic glucose production resulting in insulin resistance. Thyrotoxicosis results in increased intestinal glucose absorption and ultimate hyperglycemia, elevated hepatic glucose turnover, raised

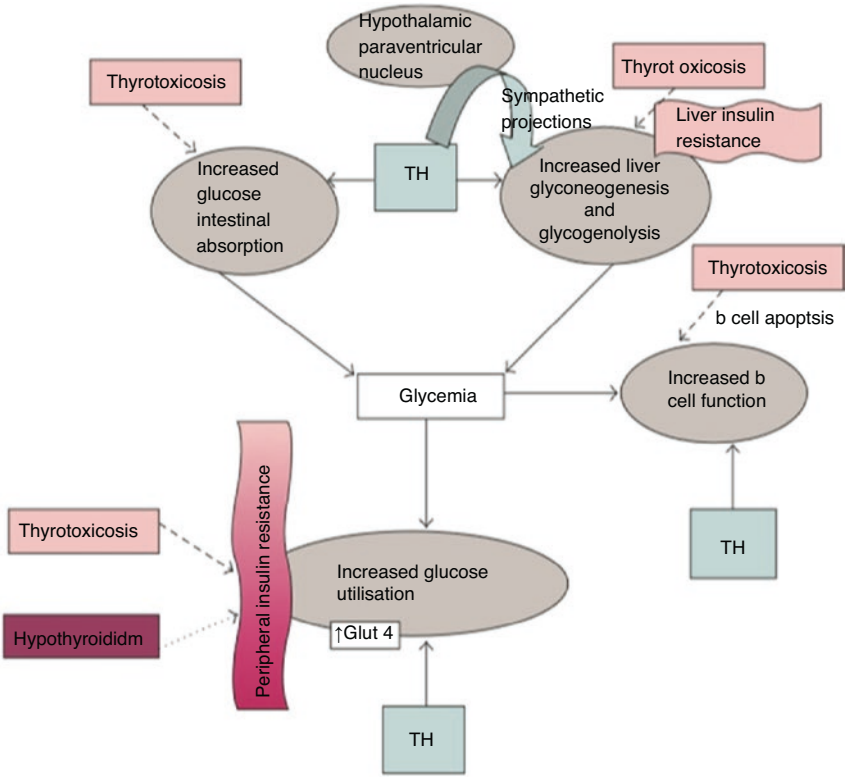

Fig. 6.3 Metabolism of glucose in euthyroid (normal), hypo- and hyperthyroidism. (Reproduction of figure is permitted by author) [21]

levels of fasting and postprandial insulin and pro-insulin leading to hyperinsulinemia, marked rise in free fatty acid concentrations. The enhanced transport and utilisation of peripheral glucose with massive increase in glucose metabolism results in non-oxidative metabolism and increased production of lactates in body. These lactates then undergo Cori cycle (lactic acid cycle) in liver and converted to glucose. However, the increased peripheral uptake is not governed by insulin in hyperthyroid patients (insulin resistance). Moreover, it has been observed that thyrotoxicosis results in apoptosis of insulin producing pancreatic β cells. It is the main pathology involved in poor glycaemic control in diabetic patients with concomitant hyperthyroidism (Fig. 6.3) [19, 20].

Hypothyroidism and Diabetes

Clinical impact of hypothyroidism in diabetic patients is less obvious as compared to hyperthyroidism. Decreased levels of thyroid hormones result in decreased intestinal absorption, decreased hepatic output and decreased peripheral glucose utilisation. The glycemic control is less difficult in diabetic patients with hypothyroidism owing to reduced hepatic glucose output, a compensation for insulin resistance in these patients (Fig. 6.3) [19, 20].

Effects of Diabetes on Thyroid Function

Poor glycaemic control in diabetic patients leads to impaired thyroid function. In diabetic individuals, the conversion of T3 to T4 is impaired resulting in low T3 state, which can be reversed with glycemic control in type II diabetes. The nocturnal levels of TSH decrease in diabetes along with reduced TSH response to TRH. Elevation of circulating insulin as a consequence of insulin resistance in diabetic patients causes thyroid enlargement and development of thyroid nodules [18, 20].

Thyroid Hormones and Lipids

Role of Thyroid Hormones in Cholesterol Biosynthesis

Lipids and cholesterols are transported across the blood with the help of lipids and protein complexes, commonly known as lipoproteins. These lipoproteins include low-density lipoproteins (LDL), very low-density lipoproteins (VLDL), and high-density lipoproteins (HDL). A transcription factor named as, sterol regulatory element binding protein (SREBP) 1and 2, regulates the expression of serum LDL receptors. The primary function of LDL receptors is to regulate blood cholesterol levels [22]. Circulating blood cholesterol is transported back to liver in a process named as reverse cholesterol transport. The enzyme hepatic lipase breaks down

HDL2 to HDL3 and enzyme lipoprotein lipase (LPL) breaks down the triglycerides to free cholesterol which is then taken up by HDL to liver. Free cholesterol is esterified to cholesteryl ester by lecithin cholesterol acyltransferase (LCAT). Cholesteryl ester transfer proteins (CETP) transport cholesteryl ester from HDL2 to triglycerides, VLDL and LDL [22]. The thyroid hormones influence the lipid metabolism in various ways. Thyroid hormones regulate cholesterol biosynthesis by influencing β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase. The T3 hormones control the LDL receptors gene activation process by binding to thyroid hormone response elements (TRE's) and also by controlling SREBP-2. Moreover, T3 up-regulates LDL receptors by protecting the oxidation of LDL. Thyroid hormones can also influence the lipoprotein metabolism and reverse transport of cholesterol by increasing the activity of certain enzymes such as CETP, LCAT, LPL, hepatic lipases. The T3 is also known to up-regulate the expression of apo lipoprotein (ApoAV), which regulates serum triglycerides levels (Fig. 6.4) [22].

Hypothyroidism and Dyslipidaemia

Overt hypothyroidism is accompanied by increased total cholesterol and LDL concentration owing to decreased activity of HMG-CoA reductase. This is due to impact of thyroid hormones on SREBP-2. Moreover, a decrease in catabolism of LDL, decreased activity of LPL and ultimate decrease in clearance of triglycerides rich lipoproteins are associated with overt hypothyroidism. Studies have also shown that hypothyroid individuals may also develop type III hyperlipoproteinemia because of increased levels of cholesterol and apo lipoproteins E, rich particles of VLDL and intermediate density lipoprotein (IDL). Elevations in the plasma level of HDL cholesterol can also be seen in hypothyroid individuals. This occurs as a result of decreased activity of CETP and an ultimate decreased conversion of HDL2 to VLDL [22, 23].

In subclinical hypothyroidism dyslipidaemia, patients are usually observed with increased total cholesterol, LDL cholesterol, increased triglycerides and decreased HDL cholesterol. Increased level of anti-thyroid antibodies, despite normal TSH levels, may also cause a rise in plasma cholesterol levels (Fig. 6.5) [22, 23].

Hyperthyroidism and Dyslipidaemia

In hyperthyroid patients, plasma levels of cholesterol decrease due to increased activity of catabolic pathways leading to enhanced synthesis and degradation of lipids. These hypolipidemic effects can be attributed to high cellular uptake and excretion of cholesterol in bile salts. Increased levels of thyroid hormones cause the accelerated lipogenesis in liver, which may lead to hypertriglyceridemia in hyperthyroid patients. Furthermore, serum LDL, HDL and subfraction HDL2 found to be

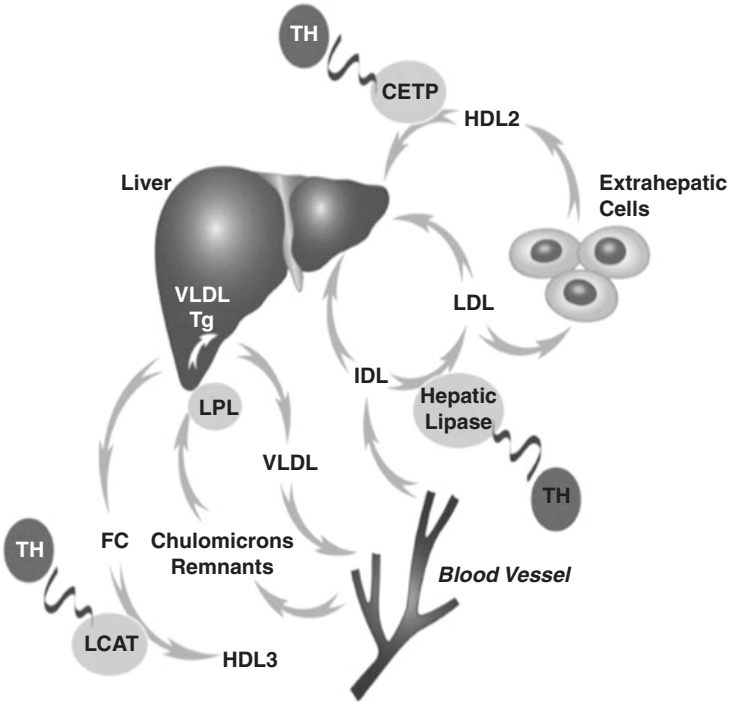

Fig. 6.4 Effect of thyroid hormones on cholesterol transport. *LPL* lipoprotein lipase; *VLDL* very low-density lipoprotein; *IDL* intermediate density lipoprotein; *HDL* high-density lipoprotein; *LCAT* lecithin cholesterol acyltransferase; *CETP* cholesteryl ester transfer proteins; *FC* free cholesterol; *HDL* high-density lipoproteins; *HL* hepatic lipase; *Tg* triglyceride; *TH* thyroid hormones. (Permission is granted by Elsevier under the license number: 4704470977456) [22]

lower in thyrotoxicosis. However, studies have shown that upon reversal of thyrotoxicosis, the lipid levels can be normalised, although the response may vary depending on pathophysiological characteristics of individuals [22, 23].

Thyroid Hormones and Bones Metabolism

Thyroid hormones have a greater influence on the skeletal development. The thyroid stimulating hormone receptors (TSHR) are also located on the surface of osteoblasts and osteoclasts. T3 hormones produce its effects on bones by chondrogenesis and mineralisation of bones. It also stimulates the interleukin 1 and 8, along with intensification of interleukin 1 and 6, augmented synthesis of osteocalcin, enhanced proliferation and differentiation of osteoblasts, and ultimate apoptosis [24].

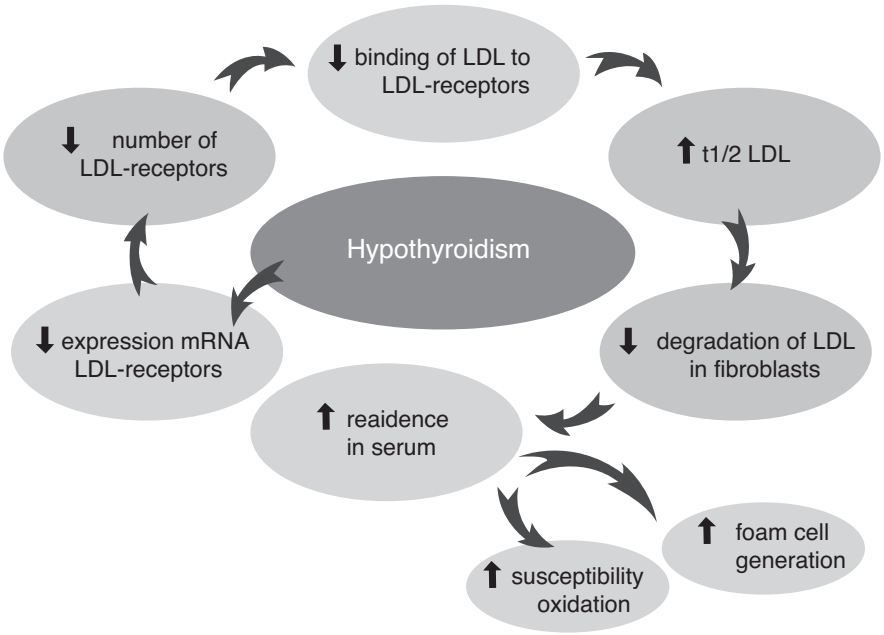

Fig. 6.5 Impact of hypothyroidism on lipid metabolism. (Permission granted by Elsevier under the license number: 4704470977456) [22]

Thyroid Dysfunction and Bone Metabolism

Increased levels of thyroid hormones result in the increased risk of fractures. It causes a marked increase in the levels of interleukin-6 (IL-6), which stimulates osteoclasts formation and ultimate less bone mineral density. This impaired bone metabolism is further aggravated by hyperthyroidism induced changes in calcium homeostasis with resultant negative calcium balance, hypercalcaemia and hypercalciuria [24]. Subclinical hyperthyroidism causes decreased bone mineral density in males and females after menopause. Hypothyroidism is also believed to have detrimental effect on bone mineral density although the underlying mechanism is not clear [24, 25].

Conclusion

Thyroid hormones regulate the cellular and intracellular functions of body by playing an important role in normal metabolic pathways. It is important to note that a bidirectional relationship exists between thyroid dysfunction and metabolic disorders such as obesity and diabetes. Obesity results in increased TRH and TSH, while diabetes causes decreased TRH response and TSH level. Insulin resistance in

diabetic patients may lead to thyroid gland enlargement and nodularity. Decreased level of thyroid hormones in hypothyroid patients may result in obesity, hypoglycaemia, type III hyperlipoproteinemia and hypercholesterolemia. While hyperthyroidism is associated with increased synthesis and degradation of lipids, hypolipidemia, hypertriglyceridemia, low levels of serum LDL and HDL, hyperinsulinemia, marked rise in fatty acid concentration in body, hyperglycemia, elevated hepatic glucose turnover, reduced bone mineral density, altered calcium homeostasis, impaired bone metabolism and greater risk of bone fractures. The clinicians should particularly alert to the possibility of thyroid dysfunctions in metabolic disorders and vice versa. All the patients with metabolic disorders should be screened for thyroid functions to prevent further complications. Further research should be carried out to observe the exact mechanism of detrimental effects of hypothyroidism on bone metabolism.

Conflict of Interest Authors declare no conflict of interest.

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Part II
Role of Endocrine Disrupting Chemicals in Metabolic Disorders

Chapter 7
Endocrine-Disrupting Chemicals: Occurrence and Exposure to the Human Being

Qurat UL Ain, Debmalya Roy, Anam Ahsan, Muhammad Asim Farooq, Md Aquib, Zahid Hussain, Brobbey Emmanuel, and Bo Wang

Abstract Endocrine-disrupting chemicals can be described as exogenous factors that impede the production, release, circulation, and binding of the body's endogenous hormones, essential for the continuation of reproduction, growth, and homeostasis. In the past few decades certain groups of chemicals that are widely used for the construction materials, home decors, and everyday use goods have demonstrated to be endocrine-disrupting chemicals which include polychlorinated biphenyls (PCBs) for electronics, paints and floor coats, fire retardants used in furniture and textiles, phthalates used in plastics and scents, parabens used for the protection of products such as lotions and sunscreens, and alkylphenols used in detergents and pesticide formulations. In several countries, endocrine-disrupting chemicals have a higher health risk and may lead to the progression of specific abnormalities. Interference with the natural hormonal mechanism causes irreversible toxicity, which creates harmful reproductive, developmental, and behavioral effects. One of the significant public health concerns of these chemical compounds is their lifelong detrimental effects. The role and impacts of endocrine disruptors and their link to

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the ecosystem and human health have already been deeply concerned over several years. However, several questions arise about the mechanisms of action of the endocrine disruptors, and further research is required. This chapter studies the current understanding of the potential health risks of endocrine-disrupting chemicals in humans and highlights a need for increasing awareness of EDCs exposure and their lifelong health effects.

Keywords Endocrine-disrupting chemicals · Exposure · Human health · Biomonitoring · Environment · Risk assessment

Background

Chemicals are a significant part of our everyday life. However, some chemicals can be proven harmful to our body's natural hormone system. Endocrine disruptors that affect the normal endocrine functions are a group of diverse chemical compounds. These endocrine chemicals have the potency to impede the physiology of the endocrine system in animals and humans. Endocrine-disrupting chemicals (EDCs) are defined by the Endocrine Society (endcrine.org) as: "an exogenous [non-natural] chemical, or a mixture of chemicals, that interferes with any aspect of hormone action [1]." In regulating critical biological processes like metabolism, breeding, growth, and behavior, the endocrine system plays a vital role [2]. More than 85 thousand chemical compounds, of which a thousand have been acknowledged as possible endocrine disruptors. A broad range of active ingredients found in different materials, including food, pesticides, plasticizers, metals, additives, personal care products, and toys, are believed to result in endocrine disruption. In everyday life, several xenobiotic compounds are used and released into the environment. These compounds can disrupt the endocrine system. Table 7.1 reports the use of some known endocrine disruptors [3]. This disruption can happen when normal levels of hormones are changed, which affect the functions of those hormones, including hormones production and metabolism, or altering the way hormones move across the body [4].

Table 7.1 Some known endocrine-disrupting chemicals and their use

Example of EDCs	Use
DDT, chlorpyrifos, atrazine, 2,4-D, glyphosate	Pesticides
Lead, phthalates, cadmium	Kids products
BPA, phthalates, phenol	Food and beverages packing materials
Brominated flame retardants, PCBs	Electronics and construction materials
Phthalates	Personal care products, medical tubings
Triclosan	Antibacterial
Perfluorochemicals	Textiles, clothing

Endocrine-disrupting chemicals are not hormones but are referred to as such because certain chemical compounds manipulate their mechanism: hormone receptors or enzyme regulation that are triggered or slowed down due to endogenous hormones. However, their effect goes far above typical hormonal routes and using several mechanisms, most of which are distinct from natural hormone pathways. Even though a broad range of mechanisms of action exists, their consequences are associated with several conditions, including infertility, cognitive abnormalities, diabetes Type-2, obesity, and cancer [5]. An endocrine disruptor can imitate or partially imitate natural hormones, including estrogens, androgens, and thyroid hormones, which may induce over-stimulation. It can also bond inside the cell to a receptor and inhibit the activation of the endogenous hormones. Upon interfering with the endocrine system, these endocrine-disrupting compounds cause harmful effects in various organ systems in the human body. (Fig. 7.1) [6]. Through the sensitive developmental phases, from fertilization to fetal development, and the growth of the baby, exposure to endocrine-disrupting compounds are of particular concern [7].

Occurrence

More chemicals are manufactured with rapid industrialization, and these manufactured chemicals then become part of our environment. Endocrine disruptors can, therefore, be discovered in food, personal care, cosmetics, pharmaceutical products, pesticides, plastics, soil, and water (precisionnutrition.com). Industrial regions are generally categorized by contamination in soil and groundwater from a diverse range of toxic chemicals. The exposure levels of identified EDCs are higher in areas where the industrial chemicals seeped through ground and water and taken up by microorganisms, plants, and then get into the kingdom Animalia. The highest proportion of these toxic substances is found in the tissues of animals at the top of the food chain, together with human beings. Upon entering the food chain, these complex mixtures gather in animals that build up the food chain, including humans and animals [8]. Table 7.2 summarizes the categories, examples, and sources of potential endocrine disruptors.

Classification

Highly heterogeneous endocrine-disrupting chemicals can be divided into two categories.

1. Naturally occurring chemicals, for example, phytoestrogen (genistein, coumestrol) and

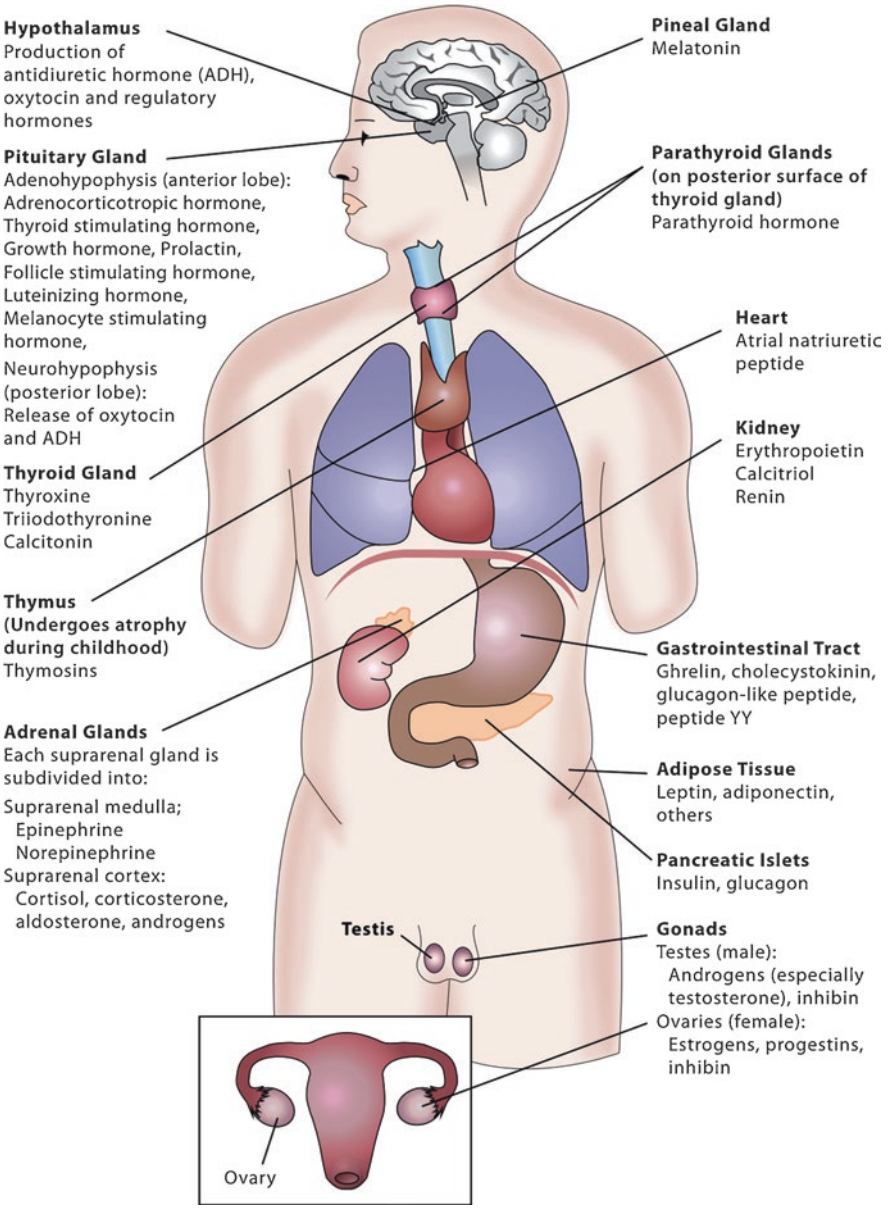

Fig. 7.1 The endocrine system comprises a number of glands located across the body (Image source: https://www.who.int/ceh/publications/endocrine/en/)

Table 7.2 Common sources of potential endocrine-disrupting chemicals

Category	Substance	Source
Polychlorinated substances from commercial production or by-products of mainly banned material)	Polychlorinated dioxins and biphenyls	Incineration, landfill
Organochlorine pesticides (present in insecticides, many have stopped now)	Dichlorodiphenyltrichloroethane, dieldrin, lindane	Agricultural groundwater/ atmospheric transport
Pesticides currently utilized	Atrazine, trifluralin, permethrin	Agricultural groundwater
Organotins (present in antifoulants used for painting ship hulls)	Tributyltin	Industrial and urban sewage
Phthalates (plasticizers)	Dibutyl phthalate, butyl benzyl phthalate	Industrial sewage
Natural hormones, synthetic steroids (present in contraceptives)	Estradiol, estrone, testosterone, estrogen	Municipal effluent Agricultural groundwater
Beauty products, personal care items, cleaners, plastics	Parabens, phthalates, glycol ethers, cyclosiloxanes, bisphenol A	Consumer products

2. Synthetic chemicals to be further categorized as:

Synthetic chemicals used for the production of industrial solvents and lubricants (polychlorinated biphenyl, polybrominated biphenyl, dioxin), plastics (bisphenol A), pesticides (dichlorodiphenyltrichloroethane), and a few pharmaceutical agents (diethylstilbestrol) [8]. The endocrine disruptors can also be listed as per their origin [9].

1. Endogenous and exogenous hormones, for example, phytoestrogens, omega-3 fatty acid, thyroid medications, and birth control tablets.
2. Medications with adverse effects on hormones (naproxen, metoprolol, and clofibrate).
3. Chemicals found in commercial and consumer products such as alkylphenol ethoxylate detergents, flame retardants, solvents, 1,4-dichlorobenzene, phthalates, and polychlorinated bis-phenols.
4. Industrial and domestic side products (dioxins, polycyclic aromatic hydrocarbons, pentachlorobenzene) [10].

The following section includes examples of commonly used endocrine disruptors from categories: food contact materials (BPA), plasticizers (phthalates), and pesticides (DDT) products. These are only some of the many well-known endocrine-disruptor sources. Other types include personal care products, textiles and clothing, and building products, among others.

Bisphenol A

BPA is a large-volume manufactured chemical; it is one of the most widely studied and most renowned endocrine disruptor. BPA was identified as an estrogen mimic, and by multiple distinct mechanisms, it can interfere with estrogen signaling [1]. BPA has been used for manufacturing certain plastic and resins. It is found in polycarbonate plastics often used in food and beverage receptacles like water bottles as well as other consumer products. BPA is also present in epoxy resin, which is used to layer the inside of metal products, such as food cans [6]. The most common human exposure to BPA is by using canned foods and drinks, BPA leaches from the cans into the food/drink. Environmental conditions, e.g., high temperature, sunlight, and acidity, boost leaching, such that acid products, like tomatoes, will leach BPA from cane linings more often. BPA leaching from the plastics to the food is enhanced by daily activities such as using plasticware for microwaving food and keeping plastic beverage bottles inside hot vehicles [1, 11].

Phthalates

Phthalates are a class of chemicals used to manufacture more elastic and difficult to break plastics, and they are also referred to as plasticizers. Phthalates are used for a broad range of products. Dibutyl phthalate (DBP), Di-2-Ethylhexyl phthalate (DEHP), and dimethyl phthalate (DMP) are among the frequently used phthalates [6]. Phthalates cause a disturbance in the production of androgen (testosterone). The young males considered as being the most susceptible to phthalates exposure since androgen, including genital growth, is critical for male development. However, androgens also play a significant part in female development, making phthalates both genders relevant. Phthalates are present in the following products: cosmetics, infant items such lotions, powders, soaps, and teethers; toys, aromatic items like candles, cleaners, and air fresheners; medical equipment like tubes, and blood bags; pharmaceutical enteric coatings; and art products. Exposure to phthalates is associated with male genital abnormalities, decreased sperm counts, endometriosis, and obesity [1].

DDT

Dichlorodiphenyltrichloroethane is an organochlorine, used as an insecticide. In the 1970s, various countries prohibited the use of DDT because of its toxicity and perseverance in animals. However, DDT is still widely used in some regions like India and Africa for killing insects that are responsible for the transmission of human diseases, e.g., dengue, malaria, and leishmaniasis. With a multitude of effects on

hormones and reproduction, DDT was among the first identified endocrine disruptors. There is a plethora of fertility issues linked with DDT. Several studies suggest that excessive DDT exposures adversely affect the fertility of both male and female. As with most endocrine-disrupting chemicals, exposure to DDT is most conspicuous for health when it occurs during the development of fetuses and childhood. DDT exposure has been proved to contributing to the early start of puberty in girls; adolescent studies suggest the prolonged menstruation and untimed menopause are also linked with exposure to DDTs, and it may cause disturbance to the menstrual cycle throughout life [12]. Based on several epidemiological studies, there is a strong link between the DDT metabolite DDE and type 2 diabetes risk [13] as shown in Fig. 7.2.

Exposure

Environmental chemicals exposure is lifelong, exposure differs depending upon people's habits and choices, and the places where they work and live. Humans are exposed to EDCs at homes, at the workplaces, in the fields, and can take up

Fig. 7.2 Endocrine disruptors and human exposure; sources and the intake routes (Image source: https://www.who.int/ceh/publications/endocrine/en/)

endocrine-disrupting chemicals by inhaling and consuming the contaminated food and water or beverages. Exposure happens through the air, water, earth, food, and other daily use products. Through ingestion, inhalation, or dermal contact, chemical toxins enter the human body and get absorbed in the bloodstream. One example of EDCs exposure is pesticides that are used to kill unwanted organisms are specially manufactured to be neurotoxic or reproductive toxicity. Invertebrates and invertebrates, the similarity of physiological mechanisms and the susceptibility of neurological and reproductive systems, indicate that the chemical compounds produced to disturb the physiological processes of one species will also harm the other, including humans [10]. Humans are primarily exposed to endocrine disruptors through food and water. It became evident that human beings, particularly children, are subjected to EDCs exposure in indoor environments such as homes, schools, kindergartens, and offices through dust and particulates. These endocrine disruptors are chemicals in appliances and electrical goods, fabrics, and furnishings. Waste and recycling management were also reported as external sources of human exposure to EDCs. Due to their hand-to-mouth behavior, toddlers and kids are highly at risk of being exposed to EDCs through intake of dust and other polluting particulates; their simple hand-to-mouth actions may result in significant ingestion of contaminated substances [14–16]. Kids on average have three times higher concentrations than adults [17]. This is likely due to exposures from breast milk and increased dust intake and close time on the ground [18]. Furthermore, they are given specific dietary habits, e.g., consuming more of their specific food group; these dietary patterns may increase exposure to chemicals in the products [19]. Regarding exposure to a potential pesticide in the general populace, food is considered a major source. However, during the application of the pesticide or the crops harvesting and storage, pesticides can also be breathed in and ingested into the body. The latter can result in higher exposures. Pharmaceutical exposure occurs through contaminated water and is most common in areas with large pharmaceutical industry and inadequate water supply monitoring [20].

E-waste (waste electrical and electronic appliances) includes several chemical substances, some of which are known endocrine disruptors. Most e-waste has a large variety of human-made chemicals, including lead, cadmium, and mercury, and organic contaminants like polychlorinated biphenyls, brominated fire retardants, and phthalates [21, 22]. The largest e-waste contributors are America, European countries, China, and Japan; however, the developing countries have significantly increased their output over the past few years. According to estimates, about 80% of e-waste is sent to the developing countries to be processed for recycling [21–23]. China is the biggest receiver of e-waste, among others, are India, Pakistan, Vietnam, and the Philippines [23–25]. Unconstrained e-waste disposal and rough recycling processes, for example, open combustion of circuit boards and wires, metal acid-stripping, plastic chipping and melting, [26] lead to the release of e-waste contaminants in the surrounding, as well as by-products of unfinished recycling procedures such as polychlorinated dibenzodioxins [27], polycyclic aromatic hydrocarbons and their halogenated homologs in addition to some other endocrine-disrupting chemicals [28]. The areas close to e-waste landfill are reported to be heavily contaminated

with harmful substances, the soil at those unauthorized dumpsites have been closely examined for the presence of chemical substances. Guiyu, South China, which is perceived as the world's largest e-waste dumpsite reported to have exceedingly high amounts of lead (Pb), cadmium (Cd), chromium (Cr), polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), polychlorinated dibenzodioxins/dibenzofurans (PCDD/Fs), and polycyclic aromatic hydrocarbons (PAH) [26]. Food and water in the surrounding areas have also become extremely contaminated. In villages alongside the rivers where e-waste dumps are destroyed, residents utilize the polluted river water for drinking, cooking, and cleaning [29]. High levels of lead and cadmium have been found in rice in the Taizhou region, which are reported to be 2–4 times higher than the permitted level (0.2 mg/k) [30]. Extreme contaminant exposure rates, via food, water, or air, have been identified in e-waste recycling areas for workers and natives [31].

Conclusion

Amid progress in several other sectors in the third world countries, there is still rather little data collected in this field. The populace subjected to endocrine disruptors in those countries and their level of toxicity are not adequately recorded and may not be accurately measured. In the future, we need to have better data about how and when the EDC act is required to avoid the occurrence of disease by reducing exposures to endocrine disruptors [7]. The chemicals list presently investigated needs to be expanded to include other materials and also chemical byproducts. EDCs' source and exposure routes should be analyzed further [32]. There needs to develop, finance, and implement our chemical strategies at the local, national, and global levels to guarantee public health [8]. To evaluate the EDCs exposure during growth periods, it is essential to develop potential biomarkers that can help to detect the EDCs susceptibility windows and early therapeutic measures can be developed. Furthermore, there should be easy to understand health information tools for public awareness. Eventually, due to the shortcomings found in clinical and epidemiological trials, the data remains complex. Even though the proof is often incomplete, the adverse effects of EDCs must be decreased.

Conflicts of Interest The authors declare no conflict of interest.

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Chapter 8
Antibiotic Resistance in EDCs-Induced Metabolic Disorders

Hina Sharif, Kanwal Rehman, Kanwal Irshad, and Muhammad Sajid Hamid Akash

Abstract Endocrine-disrupting chemicals (EDCs) possess a significant risk to humans and have a negative influence on human health. Some EDCs can act like "hormone mimics," some can block natural hormones from their activity, while some can enhance or reduce the blood harmone level, thus interfering with the body's normal metabolism. Obesity, diabetes, hyperlipidemia, and metabolic syndrome are all potentially sensitive to EDCs. Another major concern currently is antibiotic resistance which is rising to an alarming level throughout the world. New mechanisms of antibiotic resistance are emerging and spreading out worldwide, threatening the clinical practice in the treatment of common infectious diseases. Antibiotic resistance can occur due to the misuse or overuse of antibiotics as well as the insufficiency of new drug development. Some pathogens are also becoming resistant in the same way with the use of antibiotics to treat infections associated with EDCs-induced metabolic disorders. This manuscript highlights the mechanism and acquisition of antibiotic resistance and their effect on metabolic disorders such as diabetes, obesity, and atherosclerosis which can ultimately result in cardiovascular diseases.

Introduction

Metabolic disorders represent any condition with insulin resistance, dyslipidemia, abdominal obesity, hypertension, and/or hyperglycemia which are the risk factors for type 2 diabetes mellitus (T2DM), cardiovascular diseases, chronic kidney diseases,

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stroke, and cancers [1]. Four important factors including poor diet, tobacco use, physical inactivity, and alcohol consumption possess a great influence on metabolic disorders [2]. Evidence from recent research, genetic background, and exposure to environmental factors also possess a contribution in developing obesity, hypertension, T2DM, and cancers [1]. Among environmental factors, an emerging class of chemicals interfering with metabolic harmone actions is the endocrine-disrupting chemicals (EDCs) which are widely present in many consumer products [3].

EDCs are described as being a heterogeneous group of exogenous chemicals which can disrupt endogenous hormones in any aspect and hence inducing metabolic disorders [4]. According to WHO, "an endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations" [5]. There are more than hundreds of chemicals having EDC activity but more important are bisphenol, chlorotriazine herbicide, organochloride, nonsteroidal synthetic estrogen, synthetic derivatives of 17β-estradiol, organochloride insecticide, plasticizers, fluorosurfactant, vinclozolin, and many more [6]. EDCs can provoke their disrupting effect even at very low exposure level, especially if exposure happens in critical developmental periods [3, 7]. Critical developmental periods may include fetal infancy, puberty stages, pregnancy, fetal life, and menopause which can have detrimental effects on individuals leading to emergence of many metabolic diseases [8, 9]. Although it may take many years since the exposure of EDCs to the clinical representation of metabolic disorder which suggests that the fallout of EDCs exposure is not directly evident [10].

Obesity, an important metabolic disorder, affects infants, children, and adults equally. According to an estimate, about one-third children are obese or overweight and more than 60% of these children will become obese adults [11, 12]. Obesity increases the risk factor for cardiovascular diseases, dyslipidemia, hypertension, liver diseases, gall bladder diseases, insulin resistance, and T2DM [13]. According to the recent data prescribed by International Diabetes Federation (IDF), diabetes is affecting almost 463 million adults worldwide [14]. The prevalence of diabetic patients will be doubled in 2025 according to WHO reports [15]. About 70% of cases affected with T2DM are obese as obesity is related with insulin resistance; however, obesity does not necessarily cause T2DM in all cases [16]. Hyperlipidemia, another metabolic disorder, is rise in the levels of blood triglycerides, phospholipids, cholesterol, or their combination, which affects almost 25% of US adults [17]. All these metabolic disorders contribute to a significant level in causing cardiovascular diseases [1].

The discovery (natural) or synthesis (synthetic) of antibiotics is one of the greatest achievements in the field of medicines [18]. Antibiotics are considered as wonder drugs that save millions of lives of all ages. They help us in preventing amputation, lessening blindness, advancement in performing surgery, enabling new cancer therapies for clinical trials, and protecting the lives of military, but as a result of antibiotic resistance, bacterial diseases have been multiplied and spread at an alarming rate. Infections and diseases that were easily remediable by using antibiotics are now becoming difficult, in fact, impossible to cure and as a result a large

number of cases are encountering severe illness and hence dying [19]. Antibiotics, thus, present an alarming threat to much of healthcare as we know it [20].

Antibiotic Resistance

Antibiotic resistance is becoming a challenging problem throughout the world which results in a high level of morbidity and mortality [21]. Antibiotic resistance is associated with overuse and/or misuse antibiotics and thus it makes common infections and/or life-threatening infection difficult or even impossible to treat [22, 23]. Antibiotic resistance can be defined as a decreased ability of an antibiotic in killing or inhibiting the growth or development of microorganisms [24]. Antibiotic resistance can be generated on two bases, clinically and microbiologically. Clinical resistance is an antimicrobial activity which is correlated with high level of therapeutic failure, for example, treating a microorganism with a drug to which that microorganism has tested resistance [20]. The second type microbiological resistance occurs due to the genetically developed resistance mechanism, maybe mutated or acquired, resulting in a microorganism resistant to antibiotics [20]. Resistance to some important microorganisms to common antibiotics and especially origination of multidrug-resistant bacteria are widening at an alarming rate [21]. Antibiotic resistance was discovered when benzylpenicillin was introduced and for the first time it was noted in 1940 in *E. coli* [25].

Mechanism of Antibiotic Resistance

Antibiotic resistance may be acquired or inherent. Acquired resistance develops when a specific bacteria gain the genes which encode a resistance mechanism through mutation of genes or due to the transfer of genetic material from other bacteria, of the same or of different species [20]. The genes of antibiotic resistance are carried on the mobile genetic elements, which may be either plasmids (circular molecules of double-stranded DNA independent of the chromosome) or maybe transposons (that are jumping genes, a mobile sequence of DNA moveable to different positions in the genome). These transfers can occur in many ways as conjugation, transduction, or transformation [20]. Bacteria are becoming resistant to antibiotics through multiple mechanisms including (a) permeability changes in the cell wall of bacteria preventing antibiotic's access to the targeted sites, (b) antibiotic's active efflux from the microbial cell, (c) antibiotic's enzymatic modifications, (d) degradation of antibiotics, (e) development of alternate metabolic pathways other than those inhibited by drugs, (f) modification of the targets of antibiotics, and (g) target enzyme's overproduction [18].

Antibiotic Resistance in EDCs-Induced Metabolic Disorders

Antibiotic Resistance in T2DM

Diabetes mellitus (DM) is a common, debilitating, chronic, and fatal metabolic disease having constantly growing prevalence worldwide. It is of two types, type 1 DM which is due to autoimmune damage of β-cells of pancreas and T2DM which is referred as a chronic disease with multifactorial etiology, including abnormal functioning of the anterior hypothalamus and pancreas, both of which can cause insulin resistance [26, 27]. Along with its clinical complications, T2DM is also associated with less response of T-cells and neutrophil functions because of altered defensive mechanisms; hence, T2DM is related to high risk of moderate and severe infection related morbidity [28]. These infections may include foot infections, gangrenous cholecystitis, urinary tract infections (UTIs), and soft tissue infections as well as osteomyelitis, cellulitis, sepsis, and peritonitis [27, 28]. The treatment for all of these infections is becoming challenging now due to the multidrug resistance (MDR) exhibited by microorganisms, the most common pathogen among them is *Escherichia coli* followed by *Proteus* species, *Klebsiella* species, *Enterobacter* species, *Pseudomonas* species, and Gram-positive organisms as *Staphylococcus aureus*, *Enterococcus* species, and group B *Streptococcus* [28]. Diabetes is also associated with higher risk of infections because of antibiotic-resistant bacteria such as vancomycin-resistant enterococci, methicillin-resistant *S. aureus*, broad spectrum β-lactamase-producing Gram-negative bacteria, carbapenam-resistant Gram-negative bacteria, and multidrug-resistant *M. tuberculosis* [27]. Figure 8.1 represents the inter-relationship between diabetes, infections, and antibiotic resistance.

Diabetic foot infection (DFI) is a very serious diabetic complication; approximately 25% of all diabetic cases have risks of foot ulcers which can get infected easily [27]. DFI is relatively treated with broad spectrum antibiotics which ultimately can promote antibiotic resistance and hence resulting in antibiotic-resistant infections. To prevent such infections, Infectious Diseases Society of America (IDSA) in 2012 recommended prescribing antibiotics guidelines for clinical practice for the diagnosis and treatment of DFI that (a) prescribe antibiotics with proven efficacy in the treatment of DFI, (b) offer coverage over common Gram-positive cocci, and (c) offer less coverage of Gram-negative pathogens [29]. Commonly prescribed empiric oral antibiotics are co-trimoxazole, clindamycin, amoxicillin–clavulanate, and levofloxacin, administered for 1–3 weeks in case of soft tissue infections and 4–6 weeks in case of non-amputated osteomyelitis [29]. To prevent diabetic infections and associated antibiotic resistance, glycemic level should be maintained strictly to assist in improving immune functions and hence diminishing the risks for frequent infections and antibiotic resistance [27].

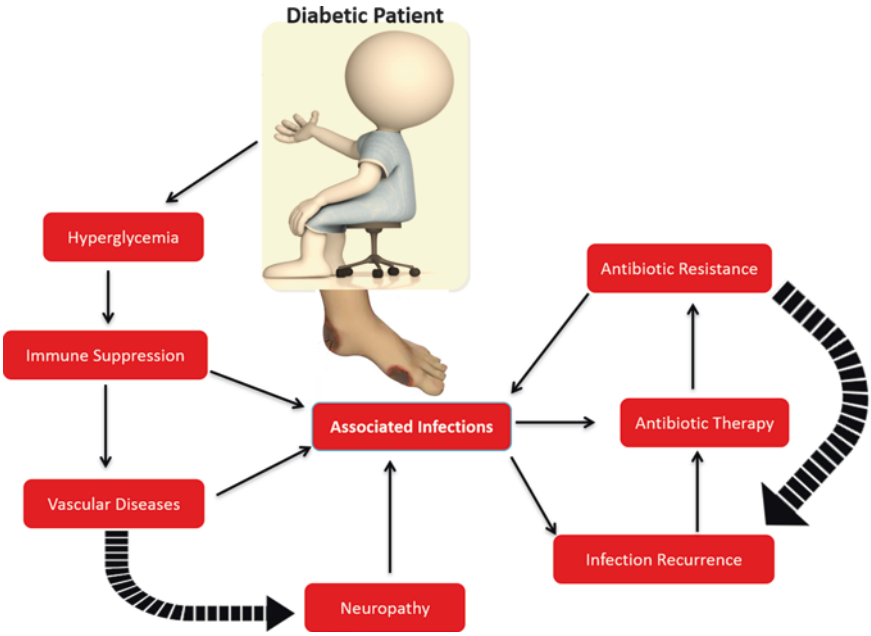

Fig. 8.1 Diabetes results in hyperglycemia and immune suppression, ultimately causing infections whose treatment with antibiotics may result in antibiotic resistance

Antibiotic Resistance in Obesity

Obesity is a major metabolic concern for both developed and developing countries as it is a risk factor of many health conditions. According to the investigations of WHO, in 2014 the global prevalence of obesity was above 600 million which was estimated to be 13% of the world's adult population and this rate is increasing at a fast rate [30]. Antibiotics are associated with changing the gut microbiota which can in turn affect the lipid metabolism and hence causing obesity [31]. As with the increase in the level of fat content and its deposition in liver, mitochondria become dysfunctional and mitochondrial dysfunction is a chief contributor in the pathogenesis of many metabolic disorders [32]. Another major outcome of obesity is insulin resistance which may be due to mitochondrial dysfunctions [33]. Mitochondrial dysfunction in obesity can ultimately lead to antibiotic resistance; hence, due to altered gut microbiota obese patients show resistance to the many antibiotics. Another research based evidence also suggests that the unregulated usage of antibiotics in early childhood can increase the vulnerability to many metabolic disorders [30]. Figure 8.2 represents the inter-relationship between obesity and misuse of antibiotics.

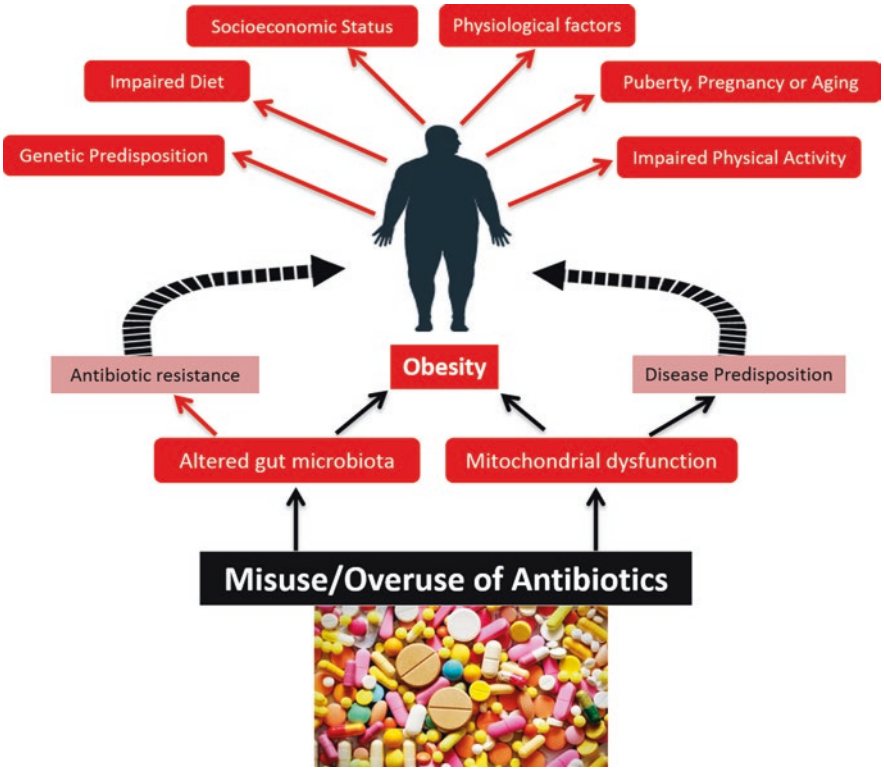

Fig. 8.2 Factors causing obesity and representation of link between obesity and unregulated use of antibiotics

Antibiotic Resistance in Cardiovascular Diseases

In the past few years, special attention has been given to the possibility of bacterial vector as risk factors of atherosclerosis which is a chronic inflammatory condition of vascular walls, because of the recently discovered intracellular pathogen *Chlamydia pneumoniae* [34, 35]. Therefore, studies on antibiotic treatment are now underway to improve the clinical condition of patients with CVDs by eradication of *C. pneumoniae* from atheromatous plaques [36]. Chlamydial infections are sensitive to tetracyclines, macrolides, and fluoroquinolones [37]. These antibiotics have generated enthusiastic expectations for proving (or disproving) the infectious-disease hypothesis of atherosclerosis and establishment of new therapies. Therefore, treatment, elimination, or prevention of vascular infections with these antibiotics might be problematic if *C. pneumoniae* which resides in circulating monocytes is antibiotic resistant. Reactivation of *C. pneumoniae* from a persistent state, promotion of

atherosclerosis, or stimulation of pro-inflammatory mediator production can occur despite the effective course of antibiotics because of antibiotic resistance [34, 35].

Conclusion

Antibiotic resistance is a global challenge which requires international actions and investment as well to preserve our existing antibiotics and development of new agents by pharmaceutical companies to address these challenges. In a similar way, EDCs are also a growing problem which can affect the health status of hundreds of thousands of humans. Therefore, this is the need of time to control the exposure of EDCs to overcome metabolic disorders and implement new policies and treatment strategies to use antibiotics to treat infectious diseases and associated antibiotic resistance.

Conflict of Interest Nothing to declare.

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Chapter 9
Alteration of Gut Microbiota in EDCs-Induced Metabolic Disorders

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Abstract There are over 10^3–10^4 microorganisms that inhabit gut microbiome. Together gut microbiome consists of 150 times more genes as compared to that of human genome. Therefore, it is considered as an "organ." Due to several factors gut dysbiosis occurs and it might result in neurobehavioral, immunological, gastrointestinal disorders, obesity, and diabetes. Changes in gut microbiota favor more pathogenic species and these species can result in producing such kind of host diseases that produce various factors that have their role in virulence, such as LPS (lipopolysaccharide). One of the most important originating factors that undergo dysbiosis in gut microbiota is endocrine-disrupting chemicals (EDCs). At present, endocrine-disrupting chemicals are found in many products that are being used in our daily life including cosmetics, plastic bottles, metal cans, toys, pesticides, and in the production of food. These EDCs impede the synthesis, secretion, transport, elimination, and activity of many natural hormones. This kind of interfering ability of EDCs can

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block or inhibit the action of hormones and finally persuade a wide range of harmful effects that may be metabolic and immunological, cardiovascular, developmental, neurological, and reproductive. The increased accumulating evidence of EDCs in our environment as persistent organic pollutants, bisphenol A, and phthalates may also illustrate their important role in the occurrence of metabolic diseases (obesity, T2D, and metabolic syndrome). This chapter will provide us information that how EDCs can influence the gut microbiome and finally lead to the development of metabolic disorders.

Keywords EDCs-induced diabetes · Gut dysbiosis · EDCs-induced obesity · Endocrine-disrupting chemicals

Introduction

In our daily lives, chemicals are considered as an essential component. But there are some chemicals that exert harmful effects on the body's endocrine (hormone) system and are known as endocrine disruptors. Only a small amount of hormones are required for their action and for the regulation of the body's development, hormones need a specific time [1]. The US Environmental Protection Agency (EPA) provides a definition of endocrine-disrupting chemicals (EDCs). According to EPA, "EDCs are the exogenous substances that modify the functions of endocrine system and subsequently can cause harmful effects to a healthy organism, or its progeny, populations, or sub-population" [2]. EDCs are known to interfere with binding actions and elimination, metabolism, transport, synthesis, and secretion. They have the ability to imitate the presence of many blood-borne hormones. EDCs contain a variety of chemicals including environmental pollutants, pesticides, and most of the compounds which are used in the consumer products and in the plastic industry [3, 4]. They are common and found everywhere on Earth. Exposure to EDCs poses significant health issues to human populations as well as wildlife [3, 4]. Some EDCs are known to have long half-lives, cannot be easily metabolized, and because of their lipophilicity [for example, organochlorine pesticides, such as heavy metals dichlorodiphenyltrichloroethane (DDT), and dioxins] can be easily reserved in the adipose tissues for years [5]. However, there are many other EDCs that can be metabolized rapidly in the human body or in the environment. They are commonly found in our daily used products like bisphenol A (BPA) which can also exert harmful effects if exposure occurs during critical period of development [3]. The concept of EDCs was proposed for the first about 20 years ago when a large number of observations about their detrimental effects on the development of reproductive system and on the gender discrimination focused on the interference of EDCs with hormones related to sex steroid [6]. Many chemicals possess properties like endocrine-disrupting chemicals, including polybrominated flame retardants, bisphenol A, perfluorinated substances, some organochlorines, polycyclic aromatic hydrocarbons, pesticides, alkylphenols, phthalates, and some household

products which contain hair dyes, cleaning products, air fresheners, cosmetics, and sunscreens. Some heavy metals even like arsenic were also shown to possess EDCs like properties. A large number of observations suggest that EDCs show a contribution to obesity, diabetes, cancer, infertility, and the metabolic syndrome [7]. In this chapter our main focus is on the metabolic disorders that are because of exposure to endocrine-disrupting chemicals. This chapter will also provide data on the alteration of gut microbiota as a result of exposure of EDCs and it will ultimately lead to metabolic disorders like obesity, diabetes, and non-alcoholic fatty liver disease.

EDCs-Induced Obesity

Obesity is accompanied by other metabolic disorders and severe health related problems which include type II diabetes, certain types of cancer, and hence, mortality [8]. Change in diet and lack of physical activity may trigger the increase in body weight although certain other factors may also have their role [9]. Furthermore, sedentary behavior in humans which involve prolonged sitting can change the endocrine and other mechanisms of chemical signaling which may promote constant weight gain in a person [10, 11]. Exposure to EDCs also has a significant contribution in the weight gain or obesity [9]. EDCs are the chemicals that produce alteration in the hormonal and other chemical signaling functions in the body [3]. Reproductive and carcinogenic effects of EDCs are mainly focused on too much exposure to endocrine-disrupting chemicals. More recent researches had emerged a hypothesis that these chemicals have their effect on weight homeostasis. However, from the investigations in the past, the adipose tissues were considered as inert storage depots, but in the 1990s, hormone leptin was discovered which suggested that adipose tissues itself are considered as active endocrine organ, releasing various adipokines and hormones and also responsible for the expression of many receptors [12, 13]. Moreover, numerous reports started to evolve that are describing excessive gain of body weight in those animals who are treated developmentally with certain EDCs which involve bisphenol A (BPA) and diethylstilbestrol (DES) [14, 15]. The exact mechanisms of EDCs-induced obesity are still under investigation because there are many potential targets of EDCs on weight homeostasis. Many of the chemicals have the ability to bind with peroxisome proliferator activated receptors (PPARs) which perform the critical roles in lipid metabolism and adipogenesis [16]. PPAR-gamma (PPARɣ), a subtype of PPARs, is a master regulator of the development of fat cells, with activation required for adipocyte maturation and differentiation [17]. The thiazolidinediones are well known as PPARɣ agonist medications that can improve insulin resistance, but they also induced obesity. Some organotin [16] and phthalates [18], which are the environmental contaminants, are PPARɣ agonists and have been associated with increased body weight in animal studies. Alteration in the adipose tissue's development itself in terms of size, number, and distribution of adipocytes formed occurs upon the in utero exposure of EDCs and it may also affect the largest regulatory systems responsible for body weight homeostasis. In animal studies,

upon exposure of oestrogenic chemicals such as bisphenol A (BPA) and diethylstilbestrol (DES) led to an increased body weight [15, 19]. Changes in expression of genes that have their role in the distribution of fat at 19 days of age occur after developmental DES exposure and it is confirmed through various animal studies [13].

EDCs-Induced Diabetes Mellitus

According to evolving evidence, it is proposed that EDCs play a vital role in the etiology of diabetes and metabolic disorders [3, 20]. From the industry side, the EDCs' effects are divided into small-exposure groups; however, the chemicals which reflect a risk for a much larger group via the food chain are coming from agro and food products. Diabetogen is defined as any chemical or chemical compound that can change the endocrine system of pancreas and metabolism of glucose. According to several epidemiological and experimental studies, it is demonstrated that a positive association exists between EDCs and hyperglycemia, insulin resistance, and glucose intolerance [3, 21–23]. The suggested mechanisms of action consist of interactions of EDCs with the aryl hydrocarbon receptor (AhR) and nuclear hormone receptors which include dysregulated hepatic metabolism, estrogen receptors, induction of oxidative and nitrosative stress, alteration in the ERK/Akt signaling pathways, and pancreatitis [24]. While accumulating data show that these molecular modes of action reinforce the effects of endocrine-disrupting chemicals on the development of diabetes. However, their exact mechanism of action is still not clarified. In the metabolism of drugs and dietary products the role of the gut microbiota is now well established, and this aspect has been covered by many different reviews [25–28]. Antidiabetic drugs are also well known for the induction of remarkable changes in the gut microbiota, and this may also suggest their antihyperglycemic effects [29]. Microbial degradation of various chemicals which also include EDCs with the help of gut microbiota can be associated with microbial dysbiosis that is a shift in the structure of microbial community, altered microbial transformation of molecules, and the induction of certain specific bacterial genes [30, 31]. Moreover, EDCs can also be transported to the liver cells, whereby EDCs can be conjugated and released into the gut via bile secretion for further microbial degradation. β-lyases, nitroreductases, azoreductases, lipases, esterases, methylases, β-glucuronidases, and thiolases are all the enzymes which are responsible for the microbial metabolism of environmental chemicals [25–28, 30, 31].

Heavy Metals

Arsenic (As) is also known as one of the recognized causative factors for metabolic disorders. According to WHO, As is considered as leading massive poisoning worldwide [32]. Several families of *Firmicute* (a bacterial phylum) were significantly

reduced upon the exposure of As, while no change was reported in *Bacteroides* levels [33]. In animal studies, As exposure induced a remarkable change in the gut microbiome and also induced alteration in the microbial metabolites. In addition to this, the composition of microbiome and metabolomic profiles in mice significantly changes when they are exposed to 10 mg/L of arsenic for 4 weeks [33]. Generally, the level of *Bacteroidetes* increases significantly but the level of *Firmicutes* decreases due to exposure of As. Lu et al. [33] had also found that these alterations were closely associated with the metabolites of bile acid, isoflavone, lipid, and indole-containing metabolites. Likewise, when chronic exposure to arsenic occurs in male mice hosts, it induced compositional and structural changes in the microbiome which is present in the colon and also promoted amino acid and nitrogen metabolism. A variety of metabolites including bile acid intermediates, isoflavones, indoles, fatty acids, glucuronides, and carnitines were significantly changed in As-exposed animal model (Table 9.1). These perturbations in metabolites reflected that capability of biotransformation in the gut microbiota also changes due to arsenic exposure [33]. The changed metabolic profile associates with altered structure of microbial community and associated metabolomics alterations are also known to affect lipogenesis, gluconeogenesis, inflammation, and adipogenesis in the male mice host [33].

Another heavy metal that was found to increase triacylglycerol level in liver, triglyceride level, and serum free fatty acids is cadmium (Cd). These changes occur upon the exposure to Cd is accompanied by a perturbation of gut microbiota (decreased *Proteobacteria* and *Firmicutes*) in animal studies. These microbial alterations led to increase the hepatic inflammation and also increase the level of LPS in serum that may further responsible for changes in energy homeostasis (Table 9.1) [34].

In male offspring, not in female offspring, lead (Pb) exposed during gestation and lactation through maternal drinking water gives rise to an increased adult bodyweight. An inverse shift in *Bacteroidetes* and *Firmicutes* ratio upon the exposure of Pb will occur and it is demonstrated through analysis that has been done on the gut microbiota of offspring without any sex bias. According to several studies it was found that the environmental chemicals have a role in shaping the adult gut microbiota when exposure to these chemicals occurs during pregnancy and also have their effect on the physiology of body (Table 9.1) [36].

Persistent Organic Pollutant (POPs)

POPs consist of dioxins, polychlorinated dibenzofurans, organochlorines, and polychlorinated biphenyls. There is a positive link between diabetes and POPs exposure which is supported by the meta-analysis of 72 various epidemiological studies [20, 39]. In animal studies, exposure of polychlorinated biphenyls (PCBs) induced significant alterations in gut microbiota with reduction in the abundance of *Proteobacteria*. It is very interesting to find that PCB-induced alterations in gut microbiota appeared to reverse by doing exercise training [40]. Exposure of

Table 9.1 Effect of EDCs on gut microbial ecophysiology and their impact on host glucose metabolism

EDCs	Changes in gut microbial diversity	Changes in gut microbial physiology	Effect on glucose metabolism	References
Arsenic (heavy metal)	No changes in *Bacteroidetes* but *Firmicutes* (*Eubacterium*, *Faecalibacterium*, and *Roseburia*) were decreased	Methylases transform arsenic into methylated derivatives. Indole-containing metabolites were significantly altered. Glucuronide metabolites and fatty acid carnitines were reduced in urine	These microbial changes can affect energy harvesting, gluconeogenesis, lipogenesis, and adipogenesis	[32, 33]
Cadmium (heavy metal)	Increase in *Bacteroides* levels and decreased *Firmicutes* and *Proteobacteria*. The changes were predominant in male mice	Increase in serum lipopolysaccharides	Increased body fat, triacylglycerol, serum levels of free fatty acids and triglycerides, and hepatic inflammation	[34, 35]
Lead (heavy metal)	Reduction in the *Firmicutes*/*Bacteroidetes* ratio. Increased *Desulfovibrionaceae, Barnesiella,* and *Clostridium XIVb* and decreased *Lactococcus*, *Enterorhabdus,* and *Caulobacterales*	–	Increased body mass and microbial changes reproducing those seen during obesity and diabetes	[36]
2,3,7,8-Tetrachloro-dibenzofuran (persistent organic pollutant)	Reduction in the *Firmicutes*/*Bacteroidetes* ratio with enrichment of *Flavobacteriia* and *Butyrivibrio* spp., and depletion of *Clostridia* and *Oscillobacter*. No dysbiosis noted in $Ahr^{-/-}$ mice	Induces fermentation of sugars and the production of SCFAs including butyrate and propionate. Production of bacterial dehalogenase that metabolizes TCDF and other halogenated compounds	Triggers inflammation and alters hepatic lipogenesis, gluconeogenesis, and glycogenolysis in an AhR-dependent manner	[37]
Bisphenol A	Causes dysbiosis with the induction of *Helicobacteraceae* and reduction of *Firmicutes* and *Clostridia*	–	Changes in microbial dysbiosis reflect the changes seen in high-sucrose and high-fat fed mice	[38]
Trichloroacetamide (disinfectant)	Decrease in the *Firmicutes*/*Bacteroides* ratio	Induction of genes associated with amino acid metabolism, energy production, and secondary metabolites, but repression of genes related to lipid metabolism. Alteration in urine metabolite profile including SCFAs	The changes in microbial and metabolite profile can influence host glucose and lipid metabolism	[37]

2,3,7,8-tetrachlorodibenzofuran (TCDF) can also induce the alterations in the gut microbiota and caused reduction in the ratio of *Firmicutes* and *Bacteroidetes*, but in $Ahr^{-/-}$mice, no dysbiosis was found [41]. TCD increased the levels *of Butyrivibrio* species and *Flavobacteria* and also decreased the levels of *Clostridia* and *Oscillobacter* species. These changes in the gut microbiota were accompanied by an enhanced bile acid metabolites (Table 9.1). *Flavobacteria* species were reported to produce an enzyme known as halogenases that can cause degradation of TCDF and other important halogenated compounds [42].

Phthalates

Phthalates are actually the esters of phthalic acid which are commonly used as emulsifying agents, dispersants, plasticizers, lubricants, and stabilizers. In personal care products which include nail polishes, cosmetics, and perfumes these chemicals are considered as the important components. Dysregulation in the metabolism of glucose, adipogenesis, and insulin resistance has been reported upon the exposure of phthalates [20, 43]. Urinary levels of phthalates in the individuals who participate in the National Health and Nutrition Examination Survey (2001–2010) showed that phthalates exposure was accompanied by a higher prevalence of diabetes, predominantly among woman—the predominant consumers of personal care products [44]. In animal model, upon exposure of diethyl phthalate led to decrease in *Firmicutes* (Bacilli) and increase in the levels of *Bacteroidetes* (Prevotella). These induced perturbations in the bacterial community were associated with consistent loss of weight in animal model that is also suggesting the role of phthalates in glucose and lipid homeostasis [45].

Bisphenol A

Bisphenol A (BPA), a commonly used plasticizer, is mainly present in our daily used plastic products which include water bottles. Bisphenol A can also contribute to the etiology of diabetes mellitus as it causes alteration in pancreatic β-cell function and lipid metabolism [20, 46]. It is very interesting to find that in animal studies, a high-fat diet or high-sucrose diet and dietary intake of BPA both are responsible for similar changes in gut microbiota. BPA can also favor the growth of *Helicobacteraceae* and *Proteobacteria*, with a decrease in the levels of *Clostridia* and *Firmicutes* (Table 9.1) [38]. These microbiota perturbations parallel the microbial structure in patients who are suffering from diabetes [47, 48]. In the development of metabolic disorders as obesity or type 2 diabetes, the prenatal exposure to BPA is considered a potential contributor. Among different studies, diabetogenic effect of BPA is considered as consistent after prenatal or perinatal exposure. The first evidence came about the diabetogenic effect of BPA from a study published in 2010 [49]. In male offspring of

6 months of age, significant alterations in pancreatic β-cell function, marked glucose intolerance, and insulin resistance have been observed upon the treatment with BPA (10 or 100 mg/kg/day) from day 9 to 16 of gestation.

Organophosphates (OPs)

OPs are also well known as a group of non-persistent chemicals which are widely used as lubricants, insecticides, oil additives, plasticizers, herbicides, and chemical weapons. These organophosphates have replaced persistent organochlorine pesticides due to their biodegradable nature. A positive association exists between OPs exposure and diabetes prevalence confirmed through several human studies [50–53]. Intestinal inhabiting bacteria such as *Enterococcus faecalis*, *Lactobacillus plantarum*, *Escherichia coli, Lactobacillus lactis,* and *Lactobacillus fermentum* were also found to degrade chlorpyrifos, a widely used OP related insecticide [54].

Conclusion

According to the significant evidence, it is stated that endocrine disruptors have their role in various disorders related to metabolism. So, it is recommended that regulatory authorities also WHO should pay attention to the production of endocrine-disrupting chemicals and their release as a policy to control metabolic disorders. The assessment of new chemicals or chemical compounds for their effects on the gut microbiota should be observed and added to the traditional toxicity assessment tests as these chemicals cause modulation of gut microbiota and provide preventive measures that how to keep itself away from the reach of these harmful chemicals. There is a small number of data supporting the field based studies. Therefore, the association of gut microbiota with EDCs and metabolic disorders remains mostly unexplored. So, to elucidate the interplay between EDCs, gut microbiota, and metabolic disorders, further research will be necessary.

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Conflict of Interest Nothing to declare.

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Chapter 10
Endocrine Disrupting Chemicals Induced Childhood Obesity

Tauqeer Hussain Mallhi, Aisha Khokhar, Yusra Habib Khan, Nasser Hadal Alotaibi, and Amjad Khan

Abstract Endocrine disrupting chemicals (EDCs) are heterogenous compounds that interfere with the conventional mechanism of endocrine system primarily through disrupting release, transfer, and production of hormones. EDCs are predominately synthetic products that are extensively found in our food, daily use products, and environment. The most commonly discovered EDCs include bisphenol A, phthalates, polychlorinated biphenyls, vinclozolin, and diethylstilbestrol. Children are susceptible to EDCs in their early life through breast milk consumption, placental transfer, and direct oral route. Due to obesogenic property of EDCs, they are capable to cause weight gain either through direct activation of adipocytes or through indirect alterations. A strong linkage is reported to exist between EDCs and childhood obesity. Bisphenol A has been broadly reported to be associated with childhood obesity. EDCs impart childhood obesity through several mechanisms including mitochondrial dysfunction and oxidative stress, peroxisome proliferator-activated receptor gamma (PPARγ), epigenetic mechanism (DNA methylation), and estrogen receptor. The most common obesogenic EDCs include bisphenols, phthalates, polychlorinated biphenyls, parabens, organotin, and non-steroidal estrogens. These obesogenic EDCs produce both short-term and long-term consequences on the overall health of children resulting in cardiovascular diseases, psychological disorders, liver diseases, breathing problems, diabetes (type 1 and 2), bone

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abnormalities, and even premature mortality. In order to avoid the aftermath of EDC induced childhood obesity, effective measures should be adopted. The most important step in the management of childhood obesity is the avoidance and removal of EDCs contributing to obesity. Furthermore, certain preventive strategies may also be adopted to keep children and pregnant females protected from the harm of EDCs.

Keywords Childhood obesity · Endocrine disrupting chemicals · Obesogens

Endocrine Disrupting Chemicals

Endocrine disrupting chemicals (EDCs) are referred to a group of extraneous chemicals which intrude the endocrine system thereby not only affecting release, production, and transport of hormones but also interfering with the binding ability, metabolism, and elimination of hormones [1]. As the environmental pollutants gained prominence gradually, the term "endocrine disruptor" was first introduced in 1991. To date, EDCs include over 1000 synthetic and naturally occurring chemical compounds [2]. The most common examples of EDCs include plastics (bisphenol A), plasticizers (phthalates), industrial products (polychlorinated biphenyls), pesticides (methoxychlor), fungicides (vinclozolin), and pharmaceutical agents (diethylstilbestrol) [3].

Classification of Endocrine Disrupting Chemicals

On account of heterogeneous nature, EDCs are broadly classified into two main categories on the basis of their occurrence and origin.

On the Basis of Occurrence

EDCs are divided into two groups on the basis of occurrence, i.e. naturally occurring EDCs and synthetic EDCs. Natural EDCs include phytoestrogen and genistein which are found in food, whereas the synthetic EDCs are synthesized and utilized in industrial products such as polybrominated biphenyls (PBB), dioxins, and bisphenol A (BPA) [4].

On the Basis of Origin

EDCs can also be grouped on the basis of their origin. It includes:

- Hormones (thyroid, omega 3 fatty acids, and contraceptive pills)
- Drugs having hormonal adverse reactions (metoprolol and naproxen)
- Routinely used chemicals in industries and homes (solvents, plasticizers, fire extinguishers, and detergents)
- Industrial by-products (polycyclic aromatic hydrocarbons and dioxins) [5]

Characteristics of Endocrine Disrupting Chemicals

Despite the fact that EDCs are considered as a group of heterogenic compounds, there are few general characteristics of EDCs, their mode of action and functioning:

- EDCs are morphologically homogeneous to most of the hormones. They possess lipophilic properties and prone to mimic the hormone action by antagonizing or activating the hormone receptors [4].
- EDCs may initiate disruption even in very low concentrations of exposure predominantly during the developmental phase. EDCs exhibit non-monotonic responses (U-shaped or biphasic), i.e. low doses produce profound impact than the higher doses in the human body [6].
- A lag phase exists between the time of exposure to EDCs and disease manifestation. It shows that the EDCs may take years to produce inimical results [4].
- EDCs exhibit low affinity for the hormone receptors, e.g. bisphenol A (BPA) shows 1000–10,000 times less affinity for estrogen receptors [7].
- The exposure time of EDCs is hypercritical in producing detrimental effects. Exposure during developmental phases such as during pregnancy, puberty, childhood, embryonic stage, and menopause is highly vulnerable [8].

History of Endocrine Disruption

The research on EDCs was initiated in mid-1991 during a conference in Wingspread Conference Center, USA by Theo Colborn and his coworkers. Theo and his coworkers gathered information from diverse fields of both humans and wildlife and developed a paradigm of EDCs. However, the traces of studies related to endocrine disruption can be found since 1940s [9]. With the advancement in public health, the concerns regarding EDCs prevailed resulting in the publication of "State of the Science of Endocrine Disrupting Chemicals" by World Health Organization in 2002.

Endocrine System and Endocrine Disrupting Chemicals

Endocrine system consists of a set of glands disseminated throughout the body. Hormones are the chemicals secreted by the glands and transferred through bloodstream to the target tissues. At the target site, these hormones stimulate action by another hormone production, alteration in metabolism or any other action depending upon the targeted receptor. Almost 50 different types of hormones manage the normal human physiology throughout life. EDCs possess similar properties as hormones and thus interfere with conventional endocrine mechanism leading to deleterious effects in both human beings and wildlife [10].

The general disrupting mechanisms of EDCs were anticipated through animal studies. The main mechanism by which EDCs interrupt cell programming is through epigenetic alterations [11]. Epigenetic alterations are referred as hereditary modifications in gene expression irrespective of any change in underlying DNA sequence. Epigenetics can modify gene expression and transcription through various pathways such as cytosine residues methylation, post-translation alteration of histones, and modification of expression on microRNA [12]. Furthermore, these epigenetic alterations may irreversibly alter the epigenome in germline resulting in the transfer of changes to successive generations. These transgenerational effects of EDCs only exist when the exposure occurs during developmental phase [13]. For instance, when a pregnant female gets exposed to EDCs, the germline of fetus (F1) also gets exposed to it. This exposed germline serves as the gametes for the next generation (F2). The successive generation (F3) will also be affected by the EDCs but through indirect exposure. The continuation of EDCs effect in F3 is considered as transgenerational [7]. Figure 10.1 illustrates the epigenetic alterations caused by EDCs [14].

Endocrine Disrupting Chemicals as Obesogens

Obesogens

Conventionally, the increase in the rate of obesity is ascribed with enhanced fat consumption and a subsequent decrease in physical activities. However, there are certain chemicals in environment that contribute towards escalating obesity rates [15]. Obesogens are referred as such chemicals that cause increase in weight either due to the direct stimulation of fat cells or through the indirect modification of the pathways that modulates appetite, satiation, metabolism, and energy balance that promotes the storage of calories [16]. Numerous known obesogens are EDCs that act through disrupting hormone receptors [17]. Several obesogenic EDCs have been involved in the development of diabetes, cardiovascular diseases, metabolic syndrome, non-fatty liver, infertility, and cancer [18]. The most common obesogenic EDCs include bisphenols, phthalates, polychlorinated biphenyls (PCBs), parabens,

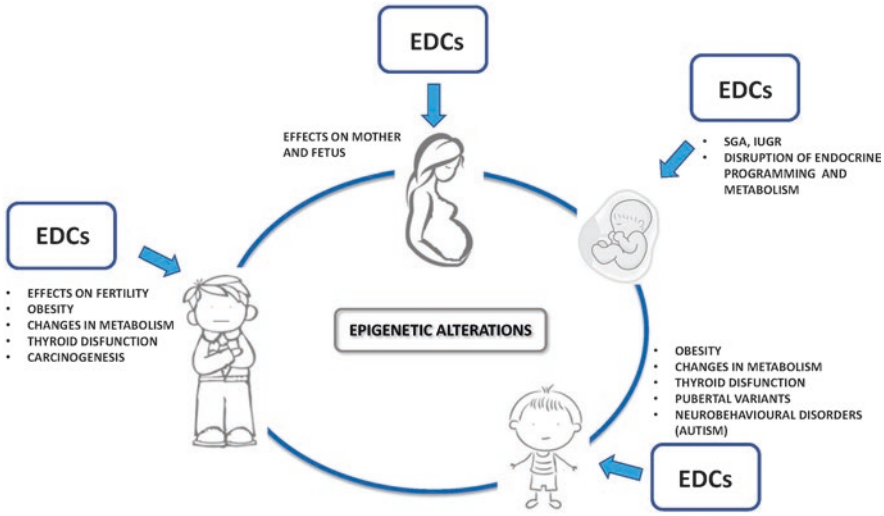

Fig. 10.1 Epigenetic alterations by endocrine disrupting chemicals (This figure is adapted from "Current Knowledge on Endocrine Disrupting Chemicals (EDCs) from Animal Biology to Humans, from Pregnancy to Adulthood," International Journal of Molecular Sciences, 2018). (Figure is not copyright protected)

organotin, and non-steroidal estrogens. The aforementioned EDCs can be the cause of obesity through affecting one of these traits:

- Hyperplasia or hypertrophy of adipose tissues
- Abnormality in adipocyte functioning
- Induction of hyperlipidemia
- Interruption in hormonal mechanism
- Enhanced preadipocyte differentiation
- Increased adipogenic differentiation of mesenchymal stem cells [19]

Association of Endocrine Disrupting Chemicals with Childhood Obesity

Childhood Obesity

According to Centers for Disease Control and Prevention (CDC), obesity in children is defined as "BMI greater or equal to 95th percentile for children and teens of the same age and sex," whereas overweight is defined as "BMI greater or equal to 85th percentile and less than 95th percentile for children and teens of the same age and sex." Globally obesity and overweight are considered to be the fifth leading cause of death in children [20]. Considering WHO statistics, the number of obese

and overweight children globally rose from 32 million in 1990 to 41 million in 2016. Childhood obesity has vulnerable long-term effects on the overall health. Obese children are more prone to develop respiratory problems, hypertension, cardiovascular diseases, insulin resistance, psychological disturbances, and fracture risks in later life [21].

Potential Obesogenic Mechanism of Endocrine Disrupting Chemicals

Several mechanisms have been hypothesized to explain the consequences of EDCs on early life obesity. It includes (a) mitochondrial dysfunction and oxidative stress, (b) peroxisome proliferator-activated receptor gamma (PPARγ), (c) epigenetic mechanism (DNA methylation), and (d) estrogen receptor [22].

Mitochondrial Dysfunction and Oxidative Stress

Mitochondrial dysfunction is one of the keystones in the development of obesity due to continuous exposure to EDCs. Through an enhanced aggregation of diacylglycerols and reactive oxygen species (ROS) mainly in insulin resistant tissues such as hepatocytes, the mitochondrial dysfunction contributes to obesity [23]. Multiple studies revealed obesity and insulin resistance in mice when exposed to PCBs due to impairment in mitochondria and adipokines level [24, 25]. Oxidative stress due to EDCs also contributes to increase in weight through lipid peroxidation and adipocyte differentiation [26]. Furthermore, the ROS accelerates the PPARγ transcription resulting in enhanced adipogenesis [27].

Peroxisome Proliferator-Activated Receptor Gamma

PPARγ is an important nuclear receptor in the initiation of adipogenesis. PPARγ is responsible for the differentiation of adipocytes, lipid metabolism, and energy balance [28]. Upon activation, PPARγ activates genes that enhance fat storage and suppress lipid metabolism genes [29]. These receptors have special binding pockets that are capable of interacting with extrinsic substances [30]. EDCs, especially mono 2-ethyl-hexyl phthalate activates numerous PPARγ target genes and induces adipogenesis [31]. BPA induces adipogenesis through PPARγ mechanism. It travels across from mother to fetus through the placental barrier. And accelerates the transcription of adipocyte genes through directly effecting PPARγ1 and PPARγ2 cell cycle transcriptional factors [32].

Epigenetic Mechanism

DNA methylation is one of the mechanisms through which EDCs induce obesity. DNA methylation is the addition of methyl groups to the DNA, resulting in the alteration of functions of DNA and gene repression [33]. Most organic pollutants and BPA are capable of initiating DNA methylation. Numerous studies had also revealed that perfluorooctane sulfonic acid (PFOS) and BPA promote adipogenesis through DNA methylation and nuclear factor erythroid 2-related factor 2 (Nrf2) pathways [33, 34].

Estrogen Receptor

EDCs also show obesogenic action through estrogen receptors. BPA is one of the first recognized estrogenic EDCs [35]. Exposure to estrogenic EDCs may modify the development of adipocytes. Although there is a scarcity of data reporting EDCs effects on human beings, animal studies report marked increase in weight on prenatal exposure to BPA [36].

Endocrine Disrupting Chemicals and Childhood Obesity: Epidemiological Evidence

There is a strong linkage between EDCs and childhood obesity. BPA has been broadly reported to be associated with childhood obesity. BPA is readily absorbed from gastrointestinal tract after oral consumption mainly through contaminated food and forms soluble conjugates after metabolism. As the newborns lack matured glucuronidase enzyme, BPA concentration is three times higher in them as compared to adults. The higher levels of BPA are mainly reported in babies using polycarbonate bottles for feeding [37]. Similarly, the measurement of BPA levels in pregnant females and their children reported a positive relationship between BPA concentration and fat mass in children [38]. Further investigations suggest that the urinary BPA concentrations in late pregnancy are correlated with leptin and adiponectin levels in newborn babies [39]. However, it was reported that among 8–11 years children, the urinary BPA concentration was directly proportional to the BMI of the children [40].

Besides BPA, phthalates are also declared to be an emerging cause of childhood obesity. Several investigations proclaimed a higher body mass index, waist circumference, and obesity with increasing urinary concentration of phthalates in children [41–43]. DDT has also been equally reported to be a source of childhood obesity. An increased prenatal DDT concentration in pregnant females and their newborn is linked with obesity in children during their early life [44]. Additionally,

Table 10.1 Route of exposure of EDCs related to childhood obesity

Endocrine disrupting chemicals	Route of exposure	Usage
Phthalates	Ingestion, respiration, dermal absorption, placental transfer	PVC plastics, toys, food, pharmaceutical, cosmetic, and baby care products
Bisphenol A (BPA)	Oral absorption, placental transfer	Consumer plastics and polycarbonate products such as feeding bottles, water bottles, plastic food containers, and cans
Triclosan	Oral and dermal absorption; placental transfer	Antimicrobial soaps, personal care products, toothpaste, cleaning products, and toys
Dichlorodiphenyltrichloroethane (DDT)	Through diet, placenta, and breastfeeding transfer	Organochlorine pesticides
Polychlorinated biphenyl (PCB)	Diet ingestion and respiration, dermal absorption, placenta, and breastfeeding transfer	Industrial products
Per- and polyfluoroalkyl substance (PFAS)	Age-related behavioral contact and diet, placenta, and breastfeeding transfer	Stain- or oil-resistant coating materials for textiles, carpet, food containers

This table is adapted from Early-Life Exposure to Endocrine Disrupting Chemicals Associates with Childhood Obesity. Annals of Pediatric Endocrinology & Metabolism. 2018. (Table is not copyright protected)

epidemiological studies unveil the involvement of triclosan, PCBs, and perfluorooctanoic acid in rapidly growing obesity in children [45–47].

Route of Exposure of Endocrine Disrupting Chemicals in Children

EDCs are predominately synthetic products that are extensively found in our food, daily use products, and environment. Children are susceptible to EDCs in their early life through breast milk consumption, placental transfer, and direct oral route [48]. Phthalates and BPA are vastly used as plasticizers to enhance durability of toys, feeding bottles, and food containers resulting in the oral absorption of these chemicals. Whereas children are exposed to triclosan through dermal route as triclosan is found in antimicrobial soaps and baby care products. Polychlorinated biphenyl and per- and polyfluoroalkyl substances are used in industrial manufacturing and transfer from mother to baby through placenta and breastfeeding. Table 10.1 summarizes the route of exposure of a few EDCs in children [22].

Impact of Childhood Obesity on the Overall Health of Children

Childhood obesity is a serious burden not only in early life but also in adulthood. The consequences of pediatric obesity are classified as short term and long term.

Short-Term Consequences

Short-term consequences occur during the period of childhood or adolescence. It is linked with multiple comorbidities such as cardiovascular risk factors, asthma, psychological disorders, chronic inflammation, and liver disease [49]. Multiple cardiovascular risk factors are linked with obesity in children. It includes hypertension, hyperlipidemia, reduced cardiac functioning, and insulin resistance [50]. It is reported that almost 58% of obese children at least possess one risk factor for cardiovascular disease. However, if multiple cardiovascular risk factors coexist in an obese child it is termed as metabolic syndrome. Obese children tend to have an increased prevalence of metabolic syndrome as compared to healthy children. In addition, the childhood obesity also accelerates the risk of asthma and respiratory problems [51].

Long-Term Consequences

Long-term consequences occur in adults who were obese during their childhood or adolescence stage. It includes cardiovascular disease, cancers, depression, arthritis, diabetes (type 1 and 2), bone abnormalities, premature mortality, and adverse socio-economic outcomes [49]. There is a dearth of evidence regarding the long-term consequences of childhood obesity on comorbidities in later life because of the lack of follow-ups. However, investigations reveal an association between adolescent obesity and destructing socio-economic status [51].

Treatment and Management of Childhood Obesity

The most important step in the management of childhood obesity is the avoidance and removal of EDCs contributing to obesity. It requires extensive knowledge about these chemicals as well as about products containing EDCs. There is little evidence available for the treatment of EDC induced childhood obesity. However, several studies have suggested the following measures to manage pediatric obesity:

- Treating families and not just the obese child
- Dietary modification using specific techniques such as traffic light diet
- Daily physical activity to avoid a sedentary lifestyle
- Weight maintenance
- Behavioral techniques to incorporate lifestyle modifications [51]

Prevention Strategies

Furthermore, certain prevention strategies can also be adopted to minimize the exposure of EDCs both in children and pregnant females. Few of these strategies are mentioned below:

- The dental fillings containing BPA should be avoided in children [52].
- The feeding bottles for child use should be BPA free [53].
- Avoid using plastics with codes #3 and #7 as they are a source of two most common EDCs, i.e. phthalates and BPA.
- Reduced consumption of canned and processed food both in children and pregnant females.
- Careful removal of old carpets and mats as they may contain PFAS [54].

Future Needs

Strengthening EDC Knowledge

It is highly important to create awareness regarding the mixture of chemicals to which humans are exposed. The scientists in particular should deeply assess features of the EDCs that disturb the endocrine system. Further research is required to discover other possible EDCs as the already known ones are just a tip of the iceberg [10].

Improved Testing for EDCs

Advanced techniques for the measurement of EDC levels should be incorporated. Presently the persistent organic pollutants are measured through gas chromatography and high-performance liquid chromatography. These techniques require a highly specific equipment and are incapable of measuring the toxic effects of EDCs in humans [55].

Projects to Reduce Exposures to EDCs

Humans and animals are continuously exposed to numerous EDCs of different chemical and physical properties. These chemicals are even present in trace amounts in our environment. By assessing the EDCs, the exposure to them can be minimized and thereby multiple metabolic disorders can be avoided effectively. The health authorities must create projects and coordinated efforts immediately to safeguard human health from the harmful exposure of EDCs [10].

Conclusion

Endocrine disrupting chemicals are steadily increasing in our environment. The children are in a vulnerable position due to continuous exposure to EDCs through toys, feeding bottles, baby care products, and food. Because of the obesogenic nature of EDCs, these chemicals are capable of inducing extensive adipogenesis in children through diverse mechanisms resulting in pediatric obesity. Although a strong association exists between EDCs and childhood obesity, there is a scarcity of data. No proper documentation is available regarding the relationship between rate of exposure to EDCs and level of toxicities in humans. Furthermore, specialized investigations are still required to be conducted in humans to better understand the effect of EDCs in obesity. With the rapid rise in childhood obesity rate owing to EDCs, rigorous efforts are promptly required to safeguard our future generations from this menace.

Conflict of Interest The authors declare that there is no conflict of interest.

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Chapter 11
Role of Polychlorinated Biphenyls as EDCs in Metabolic Disorders

Waseem Hassan, Hammad Ahmed, Ghulam Murtaza, Muhammad Ihtisham Umar, and Furqan Muhammad Iqbal

Abstract Polychlorinated biphenyls (PCBs) are the aromatic hexagonal biphenyl compounds bonded with the chlorine atoms. These are hazardous compounds, which come in contact via inhalation or skin contact. There is the notable number of exposure incidence reported in different parts of the world. Often the consequences of exposure were proved to be very lethal resulting into the number of deaths. PCBs can be divided into two groups including dioxin-like and non-dioxin like PCBs. They are distributed primarily in adipose tissues and excreted through urine after metabolized in the liver. PCBs can react with several nuclear receptors that are influencing lipid metabolism. The nuclear receptors comprise of Aryl hydrocarbon receptor (AhR), constitutive androstane receptor (CAR), and pregnane xenobiotic receptor (PXR). PCB is reported to cause metabolic disorder including hepatic steatosis, obesity, diabetes mellitus, endocrine metabolism, thyroid metabolism, and dyslipidemia. It has been observed that the antioxidants containing diet can help to control the toxic effects of PCBs.

Keywords Polychlorinated biphenyls · Metabolic disorders · Nuclear receptors

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Abbreviations

AhR	Aryl hydrocarbon receptor
ARNT	Aryl hydrocarbon receptor nuclear translocator
CAR	Constitutive androstane receptor
CPT1 and CPT2	Carnitine palmitoyltransferase I and II
CVD	Cardiovascular disease
IARC	International Agency for Research on Cancer
LDL	Low-density lipoproteins
LEPR	Leptin receptor
MRC	Complexes mitochondrial respiratory chain complex
mtFA	Mitochondrial transcription factor A
OXPHOS	Oxidative phosphorylation
PCBs	Polychlorinated biphenyls
PON1	Paraoxonase 1
POP	Persistent organic pollutants
RRAD	Ras-related associated with diabetes
TC	Total cholesterol
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TG	Triglycerides

Introduction

Polychlorinated biphenyls (PCBs) have been used in industry since 1929 [1], arising exclusively from anthropogenic origin. The backbone of the chemical structure is biphenyl hexagonal carbon rings. The carbon atoms share electrons, forming a couple of hexagonal rings that result in biphenyl which is an "aromatic" compound. More than 200 possible chemical structures can be formed by adding or removing the chlorine atoms at different positions of the biphenyl rings. There are more than 200 chemical structures that are labelled as congeners [2].

In Slovakia, inappropriate dumping from the Chemko factory resulted in the release of PCB containing effluent into the Laborec River, resulting in its sediment contamination which remains so up till today [3]. Japanese Yushu poisoning in 1968, Yu Chen incident in Taiwan [4, 5] and a PCB/dioxin incident in Belgium 1999 are a few of the other known examples of such poisonings [6, 7], causing the great number of human casualties. Dioxin is a component of an Agent Orange, which was used during the Vietnam War. In 1976 a catastrophic Seveso tragedy in Italy, a massive quantity of dioxin was released in the environment resulting in several industrial accidents [8]. PCBs can be subdivided into groups either of the degree of chlorination or number of chlorine atoms in a biphenyl molecule, i.e. three chlorines (trichloro) and four chlorines (tetrachloro) [9].

Occurrence

PCBs are extensively used as plasticizers in cement and paints industry, wax extenders, coolants and insulating fluids, and flame retardants. According to the occurrence PCBs are divided into dioxin and non-dioxin-like compounds. Depending on the similarity with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Examples include 3,3′,4,4′-tetrachlorobiphenyl (PCB 77) and 3,3′,4,4′,5-pentachlorobiphenyl (PCB 126). PCBs are also produced in large scale industries, which are known as famous Aroclors. Because of having a potential of environmental toxicity and considered as persistent organic pollutants (POPs), their manufacturing was banned by the Stockholm Convention on POPs in 2001. The International Agency for Research on Cancer (IARC) classified PCBs as Group 1 carcinogens in humans. Although the levels of PCBs are diminishing in the atmosphere due to their limited use but their acquaintance still considered harmful [10]. PCBs are known to cause and contribute to glucose and lipid metabolic disorders including hypertension, diabetes, obesity, and NAFLD in exposed humans [11, 12]. In animal studies, it is confirmed that it can induce steatosis and steatohepatitis [10, 12].

Chemical Structure

Chemical structures of certain PCBs are shown in Fig. 11.1. Meanwhile, chlorine atom is the foremost part of the group, though other halogens can also form a bond with biphenyls. PCBs are composed of up to 50 or 60 congeners (or individual chlorobiphenyls). Mixtures are formed by the reaction of unique compositions at specified reaction conditions. Their composition results in the formation of specific congeners, thus different proportions of these congeners used in industrial mixtures. These mixtures are found in liquid to viscous turbid solids [13]. The industrial manufacture of these mixtures was forbidden in the USA (between 1930 and 1977) as only Monsanto companies were solely producing these chemicals under the commercial name of Aroclors (*Aro*: Aromatic *clor*: Chlorine). Each Aroclor is coded by number (e.g., Aroclor 1242, 1248, and 1254), the last two numbers usually denote the percentage of chlorine by weight in the composition. For example, Aroclor 1248 contains 48% chlorine by weight. Furthermore, PCBs are marketed in different commercial names in several countries like Clophens (Germany), Soval (Soviet Union), Santotherm (Japan), Phenolclor (France), Pyralene (France), Fenclor (Italy), and Kanechlor (Japan). It is noteworthy that Aroclor is also the trade name of the other halogenated biphenyls [14].

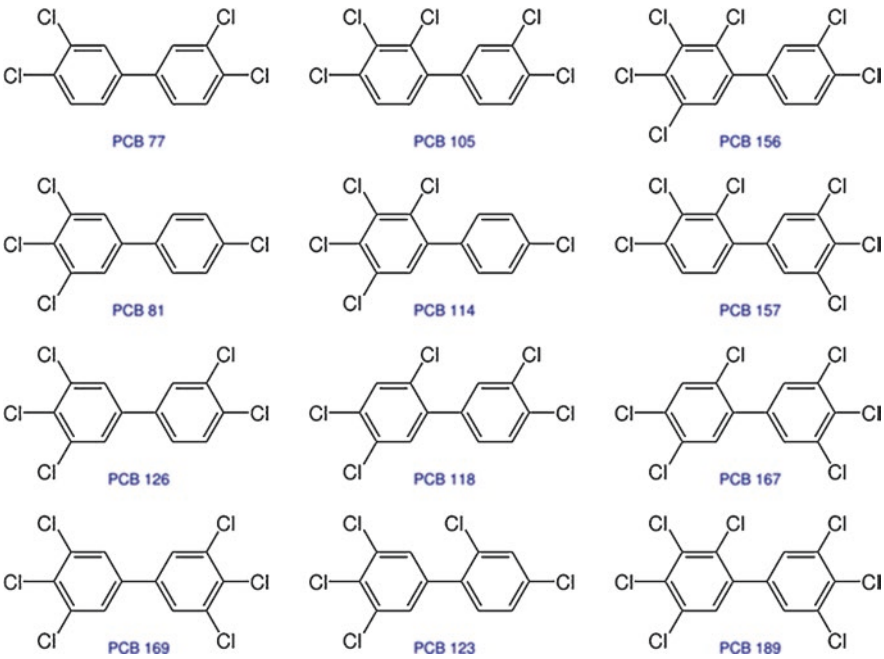

Fig. 11.1 Examples of PCB homologues

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)

The most abundant PCB in the environment is TCDD. It is also composed of biphenyl aromatic rings along with four chlorine atoms attached to respective positions. This is a by-product during organic synthesis and waste combustion. The intoxication of TCDD leads to several harmful effects, including severe skin lesions such as chloracne, dehydration, weight loss, peripheral neuropathy, and hepatotoxicity [8, 15]. Chronic intoxication by TCDD allegedly causes dyslipidemia, atherosclerosis, hypertension, diabetes, chronic liver disease, and various types of cancers [16]. Moreover, TCDD is considered as a Group 1 carcinogen by IARC. A study on the exposure of TCDD in humans showed increased plasma transaminases, steatosis, fibrosis, and inflammation, are associated with the steatohepatitis in some individuals [8, 15].

Exposure of PCBs: Pharmacokinetics and Pharmacodynamics

Humans are exposed to PCBs by oral, inhalation, and skin routes. While PCBs are readily absorbed, they have slow metabolism resulting in slow excretion. However, they distribute and accumulate widely in the liver and muscle tissues. PCBs are

lipophilic in nature, lipophilicity depends on the number of chlorine molecules in the biphenyl ring. Owing to this high lipophilic nature especially the highly chlorinated congeners, tend to accumulate in lipid-rich tissues. More amounts of PCBs are usually found in adipose tissue, breast milk, liver, and skin [17]. PCBs can enter the nucleus of the cells and binds with numerous nuclear receptors especially that are associated with lipid metabolism, such as Aryl hydrocarbon receptor (AhR), Constitutive Androstane Receptor (CAR), and Pregnane Xenobiotic Receptor (PXR) [18]. Multiple studies are carried out to ascertain the half-lives of the PCBs. It was assessed to be 21.83 and 133.33 years for Aroclor 1242 and Aroclor 1254, respectively. However, half-lives of both lower Aroclor 1242 and higher Aroclor 1254 chlorinated biphenyls are 2.6 and 4.6 years, respectively [19].

The metabolism entirely depends on the degree and orientation of chlorination on the biphenyl rings. They are predominantly metabolized in the liver by cytochrome P-450 system into phenols. In phase 2 of the metabolism hydroxylation and conjugation of the metobilites with glucuronic acid and sulfates occured, hence further hydroxylation results into the formation of catechol [20]. Glucuronide and sulfate conjugates are excreted in the urine and hydroxylated metabolites are excreted in the bile. Generally, metabolism of the less-chlorinated congeners are comparatively more rapid. This is also one of the explanations that highly chlorinated congeners tend to remain in the body longer than do less-chlorinated congeners. Conjugation and glucuronidation tend to polarize the PCBs which ultimately facilitate the elimination by fecal and urinary route [21].

Hepatic Steatosis

The mechanisms through which PCBs can cause hepatic steatosis are still not understood very well and most probably differ between compounds. Although activation of AhR can lead to hepatic steatosis by several mechanisms. Several *in vitro* studies proved mitochondrial dysfunction as a result of their exposure primarily at the level of Mitochondrial Respiratory Chain complex (MRC complexes), Oxidative Phosphorylation (OXPHOS), and mitochondrial transcription factor A (mtFA) [22–25]. These hazardous effects are mostly observed at high concentrations of PCBs (>10–20 μM). Certain experimental studies reported that some PCBs can cause fatty liver diseases [26–28]. Possible mechanism of fatty liver disease is the reduction in hepatic PPARα expression. Their expression was associated by a robust reduction of Carnitine palmitoyltransferase I and II (CPT1 and CPT2) expression [28]. Erstwhile reported that small concentration (i.e., 1 nM) of PCBs have the ability to strongly decrease PPARα mRNA expression [29].

Steatosis having necro-inflammation and fibrosis is regularly observed in intoxicated animals, [30–34] confirming TCDD potential of steatohepatitis. Mechanism of TCDD-induced steatosis includes raised fatty acid uptake in liver, decreased VLDL secretion, and reduced mtFAO [35, 36]. All these effects are completed through AhR activation [37, 38]. TCDD has the potential to diminish the activity of

different MRC complexes, which could take part in mitochondrial ROS production [39–41]. However, TCDD caused excessive mitochondrial ROS production appears to be the factor that activates AhR [42]. It also promotes liver fibrosis development in high fat diet obese mice [43].

Obesity

Chronic exposure to PCBs causes obesity; the possible effects are endocrine disruptors on body weight. The exposure of PCBs also causes obesity in children [44]. PCBs act by altering the AhR expression of principal genes correlated to adipogenesis, lipid metabolism, and inflammatory factors [45]. Leptin Receptor (LEPR), Ras-Related Associated with Diabetes (RRAD), Aryl hydrocarbon receptor nuclear translocator (ARNT), and Paraoxonase 1 (PON1) are the most common receptor and genes that plays significant role in the obesity. Abnormality of these receptors is observed among highly exposed subjects [46]. PCBs readily cross the placental barrier. It can harm developing neonates. Prenatal exposure of the PCBs can also cause obesity in children [5, 47]. Prenatal exposure of certain PCBs can be the reason of smaller size at birth [48]. Early exposure of PCBs in pregnant women can be a predisposing factor for the development of obesity in future [49].

Diabetes Mellitus

PCBs have the potential to directly alter glucose homeostasis and cause diabetes [50]. In the US, it is observed that PCBs exposure is linked with an escalation in β-cell function, resulting in hyperinsulinemia and insulin resistance [51]. Beta-cells of the pancreas lack the antioxidant potential. This oxidant stress mediates the reactive oxygen and nitrogen species that ruin their function by modifying metabolism and/or ATP sensitive potassium channel activity while inducing apoptosis [52]. Chronic exposure to the PCBs causes insulin resistance and hyperinsulinemia leading to diabetes mellitus [53]. Increased serum concentrations can lead to type II diabetes [54]. The exposure of PCBs in the elderly age increased the likelihood of diabetes [55].

TCDD reduces glucose-stimulation and insulin release in animal models, similar effects were observe in AhR knock-out mice [56]. TCDD exposed rats had depleted islets of langerhans [57], similarly the depletion of islets is detected during the long lasting exposure to PCBs [58]. Due to the depletion of islets, the insulin secretory effects resulted in a diminution of cellular insulin level [59] and TCDD anticipated to promote β-cell “exhaustion” [60]. This recommends that chronic extended exposure of these compounds could result in deficit of insulin.

Table 11.1 Showing the effects of PCBs on the different sex hormones [63–69]

Hormone	Parameter	Effect	Species
Progesterone	Plasma concentration	Decreased	Rat
	Metabolism	Increased	Rat
	Half life	Decreased	Rat
	LH induced synthesis	Increased	–
Estrogen	Binding to the uterine receptor	Decreased	Rat
Testosterone	Metabolism	Increased	Rat
Corticosterone	Plasma concentration	Increased	Rat
		Decreased	Mouse
Androstenedione	Metabolism	Increased	–

Aroclor 1260 causes glucose tolerance, insulin resistance/sensitivity, adipokines, pancreatic insulin secretion, and hepatic gluconeogenesis [61]. Intranasal exposure encouraged insulin resistance in rats, hyperinsulinemia, and hypertriglyceridemia together with increased oxidative stress on the islets of Langerhans [62].

Endocrine Metabolism

The underlying cause of the reproductive toxicities of PCBs is the alteration in the hormonal levels or receptor affinities level. Decreased level of the hormone is due to an increase in the metabolism of the steroids which are the normal substrate of the microsomal enzymes (Table 11.1).

Thyroid Metabolism

PCB impairs the kinetics of the thyroid hormone metabolism and causes hypothyroidism [70]. Certain PCBs are structurally similar with thyroxine [71]. During pregnancy the PCBs exposure significantly crosses the placental barrier that competes with thyroxine (T4) for plasma transthyretin binding sites [71]. Thyroid hormones are essential for usual development of the being. Disturbance in the levels of thyroid hormone during the pregnancy may lead to structural and functional aspects of normal development of the brain and sexual organs. Hypothyroidism may impair the growth in the developing brain [72]. While in the Seveso accident, exposure of TCDD increased the incidents of thyroid cancer especially in women [73]. Variations in serum thyroxine levels were also detected, subsequent occupational or accidental exposure [74].

Dyslipidemia

Dyslipidemia is characterized by lipid anomalies that can lead to the development of cardiovascular disease (CVD). A change in the lipid metabolism leads to the development of CVD, lifestyle changes are the hallmark to treat and prevent dyslipidemia. Most commonly used pharmacological therapies include the statins and fibrates [75–77]. The aim is to prevent cholesterol synthesis by inhibiting the HMG-CoA reductase enzyme [78, 79]. Laboratory studies have proved the association between hyperlipidemia and PCB exposure [80–82]. PCB 77 displayed increased serum cholesterol levels [83]. Epidemiological studies suggesting PCBs exposure cause dyslipidemia [84, 85]. It can also elevate triglyceride levels [85–91]. PCB increases both LDL and TC [90, 92], however, decreases the level of HDL (good cholesterol) [88, 93]. It is well reported that increased levels of HDL decrease the risk of CVD [94].

The AhR has established a significant role in the development and function of the CVD [95]. It is also observed that increased expression of AhR is observed in CVD patients [96]. TCDD increases blood pressure following an AhR mediated pathway [97]. It is suggested that PCBs are capable of inducing hypertension. Exposure to PCBs also increases the aldosterone production [98–100], which was attributed to increases in CYP11B2 (aldosterone synthase) expression that was free of AhR activation [100].

Conclusion

PCBs have the capability to cause numerous metabolic disorders. Epidemiological and animal research has revealed that PCBs can lead to metabolic disorders like hepatic steatosis, obesity, diabetes (type 1 and 2), dyslipidemia, thyroid and endocrine metabolism. Interestingly, these conditions are isolated risk factors for developing multiple diseases like liver carcinoma, chronic diabetes, and cardiovascular diseases. People residing near and around the industrial, hazardous waste site have increased risk of these diseases. It is important to recognize several ways to curtail and avoid PCBs toxicity. Since PCBs are lipophilic, and accumulate in tissues, the people who are more at risk of exposure to these toxins should properly be educated and regularly checked for the possible disease. Abundantly antioxidants containing diet and a decent lifestyle can help counter the unwanted effects of PCBs [101–103]. High fat diet may decline overall fat burden by enhancing elimination rates, subsequently decreasing the accumulation of PCBs in the body [104]. Importantly, the research should continue to open new horizons to identify and minimize the toxic effects of the PCBs.

Conflict of Interest Authors declare no conflict of interest.

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Chapter 12
Role of Furans as EDCs in Metabolic Disorders

Saima Muzammil, Asma Ashraf, Aqsa Muzammil, Rahat Andleeb, and Azhar Rafique

Abstract Furan is common compound that can be found in many products in pure form and as its derivatives. It is abundant in environment as in processed food, industrial process, pharmaceutical products and smoke. When furans are heated, they enhanced oxidative processes in lipids and proteins, and therefore play a toxic role in many cases. In many body systems furans are examined to cause toxic effects. It is commonly formed from four precursors amino acids, carbohydrates, ascorbic acids and PUFA. To detect the presence of furan and its amount in sample many methods have been involved. Most common of them are headspace analysis, headspace sampling by solid phase microextraction, and GCMS. As furan toxic effect is confirmed in many animals and it can be harmful to human health as well. The quantity of furan taken by humans are measured through quantification of furan in many food products. Many health agencies such as EFSA, FDA and IARC determine amount of furan in different foods. Further experiments were conducted to determine its harmful effects. Mouse and rats were mostly used in such tests. In rat metabolism of furan is tested and recorded that 80% of furan was eliminated through different pathways. Furan affects on digestive track is also determined. It mostly affects liver due to its prolonged presence in liver, but it was also observed to be harmful for kidneys. Some products are also tested to mitigate furan toxicity, apigenin and lycopene were found to be effective against furan toxicity. Moreover, furan itself was known to be effective against oxidative stress, which may cause many neurodegenerative disorders.

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Keywords Furan toxicity · Furan effect on liver and kidney · Furan detection method · Furan health concerns

Introduction

Endocrine Disrupting Compound (EDC) is defined in a simple way as exogenous chemicals that could have disturbed the human endocrine system. This disturbance in the endocrine system caused the hormonal imbalance, which leads to many metabolic, reproductive and developmental diseases [1]. Endocrine Disrupting Compounds (EDCs) are defined in details by many agencies and U.S Environmental Protection Agency definition of EDC is "an exogenous agent that interferes with syntheses, secretion, transport, metabolism, binding action or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis reproduction, and developmental process." It is considered that EDCs alter the hormones receptors, for instance, oestrogen receptors (ERs) progesterone receptors, androgen receptor (AR) and thyroid receptors [1]. We are exposed to EDCs by different means, including food intake, contaminated air and directly exposed to EDCs chemicals. These chemicals possibly invade to the food chain and concentrated on animal tissues as well as humans. EDCs are commonly piled up in adipose tissues, because of their lipophilic nature, and generally, possess longer half-life. EDCs compounds can be classified into many categories. These chemicals pharmaceutical agents, a synthetic chemical used in industries, its by-product, pesticides and fungicides. Among many endocrine disruptors, furan is one of the EDCs and have its consequences on the human health system [1].

What Is Furan?

Furan having the chemical formula (C4H4O) formed a heterocyclic compound of the five-sided ring. This aromatic ring having four carbon atoms and one oxygen atom. Furan molecular weight is computed to be 68. A very low boiling point of furan, 31 °C [2], ensured its high volatility [3]. Furan is used in the industrial process because of the accessibility of its parent and derivatives cyclic compounds. It has drawn attention as a result of the development of new synthetic strategies. Some of the most common furan and its derivatives used in industries are shown in Fig. 12.1 [4].

In water, synthetic and herbal medicines, industrial processes and the environment, furan-containing compounds are abundant [5]. From an industrial point of view, furan is known as an intermediate compound for manufacturing of many

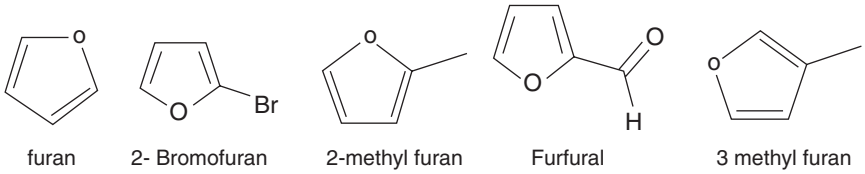


Fig. 12.1 Furan and its common derivatives

chemicals like lacquers, resins, drugs and pesticides, thiophene, tetrahydrofuran and pyrolean synthesis. Many foods can act as precursor of furan formation when heated, especially foods comprising sugar, carotene, vitamin C and amino acids [6]. In addition, furan is considered a by-product of high energy radiation and thermal processes in food production [7]. Furan products are also used as flavouring factors in certain products and tobacco processing [8]. Furan is known to enhance oxidative processes in lipids and proteins when heated, by influencing free radicals and antioxidant defence [9]. Several of these chemicals are harmful and trigger problems if human contact is possible. Minor changes in composition influence the target organ and the toxicity found.

Occurrence of furan is evaluated, using 17,056 analytical results, in different age groups and assessed to be highest in infants. The calculated mean dietary exposures were 0.14–0.99 lg/kg of body weight in infants. The susceptibility is driven primarily by coffee for adults. Food group consists of grains and their products are regarded as highest, contributor of furan exposure in children and teenagers and the second most important in all other age groups. The effect of furan concentrations by heating of processed foods is associated with consumer behaviour. Overall exposure assessment of furan formation during home cooking was not influenced by specific scenario such as toasting bread. However, the addition of methyl furans may gain interest significantly or the exposure calculation the sum of furan, 2-methylfuran and 3-methylfuran is estimated to be highest in adults and elderly as compared to the baseline. The main reason for higher exposure was the large concentrations of 2-methylfuran present in coffee (four times higher than furan) [10]. Thus, in various body systems, we examined existing evidence of toxicity of furan and its active metabolite and derive bioassay data from it. This can be used to evaluate health risk such as cancer from furan toxicity. Figure 12.2 shows thermally processed food role in cancer via 5-hydroxymethylfurfural metabolism.

Furan though used in many industries has toxic effects and also form many other toxic compounds. Furan and its derivatives can be found in many natural and synthetic sources and can have both kinds of toxic and non-toxic effect. In the environment, furan can be found in smog, car exhaust and smoke from wood and tobacco as a result of incomplete combustion. Furan also present in food and pharmaceutical products. We have summarized the derivatives of furan, their sources and its toxicity in Table 12.1.

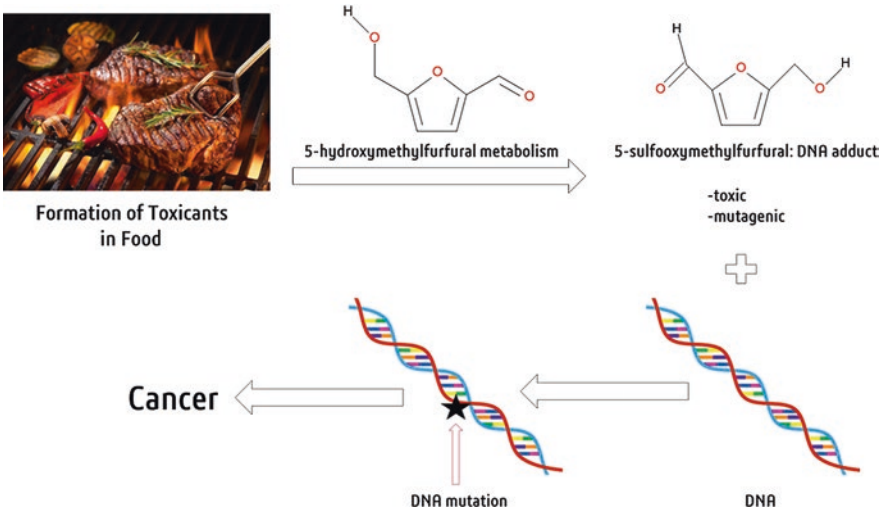


Fig. 12.2 Role of thermally processed foodstuffs in causing cancer on the example of 5-hydroxy methyl furfural metabolism

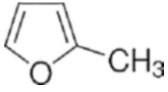
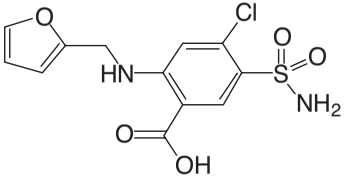
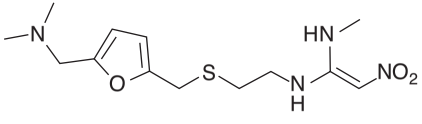
Mechanism of Formation Furan and Methyl Furan Precursors in Food

The combination of food by-products, including amino acids, ascorbic acid, carotenoids, carbohydrates and unsaturated fatty acids, can produce furan. The pathways described below were investigated and confirmed for foods in model systems. Furan is formed by using various paths and different precursors. Furan formation pathways are as follow:

1. Furan via amino acids thermal degradation.
2. Furan via ascorbic acids oxidation.
3. Furan via oxidation of PUFA and carotenoids.
4. Furan through degradation of Carbohydrates.

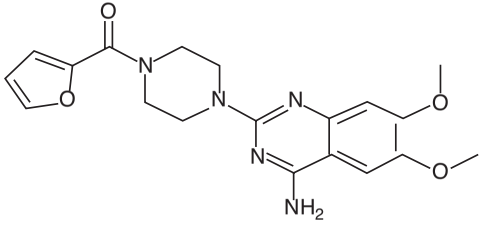
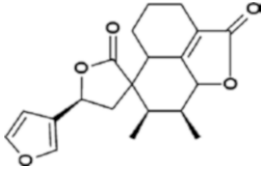
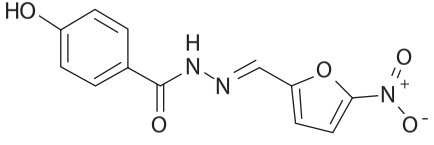
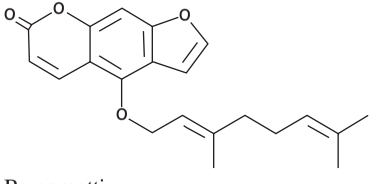
From thermal degradation, furan is formed utilizing ascorbic acids as precursors and in some cases, ascorbic acids derivatives can also be used as precursors. In Maillard reaction, that is very common in furan formation, lipids, reducing sugars, amino acids and organic acids are used [28, 30–32]. The furan formation mechanism was studied by [33] in that study they labelled the carbon atom 13C3 in different precursors such as sugar, amino acids and ascorbic acids. These were then heat-treated at 25 °C and furan formation was measured by each of these precursors. From reaction mixture, the highest concentration of furan was observed in ascorbic acids and its derivatives. These findings were again confirmed by [34] experiments and established that ascorbic acids are the best candidate for formation of furan.

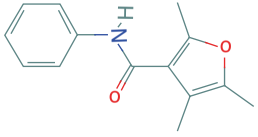
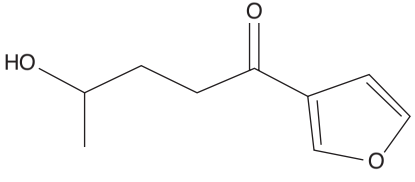
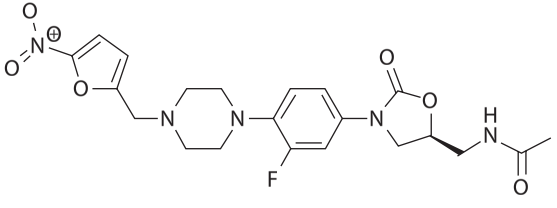
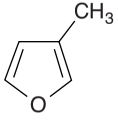
Table 12.1 Furan and furan derivatives from different sources and its toxicity

Furan or derivatives	Source	Toxicity	References
 Furan	Processed food, smog, wood, car exhaust	Carcinogen when taken orally. Liver toxicant in rat and mouse	[3, 11–15]
 2-Methylfuran	Food, coffee, tobacco smoke	Lung toxicant in rat	[14, 16]
 Furosemide	Pharmaceutical	Non-toxic to human at therapeutic dose	[17, 18]
 Ranitidine	Pharmaceutical		

(continued)

Table 12.1 (continued)

Furan or derivatives	Source	Toxicity	References
 Prazosin	Pharmaceutical	Non-toxic	[19]
 Teucrin A	Germander extract	Human and Mouse liver toxicant	[20, 21]
 Nifuroxazide	Pharmaceutical		
 Bergamottin	Grapefruit Juice	Inactivator of P450	[22–25]

 Methofuroxam	Fungicide		
 4-Ipomeanol	Mouldy sweet potatoes product	Lung toxicity showed in animal lab. Human liver toxicant	[26, 27]
 Ranbezolid	Pharmaceutical		
 3-Methylfuran	Air pollution, food, tobacco smoke, mould metabolites	Lungs toxicants when inhaled	[28, 29]

Furan Formation via Amino Acids Thermal Degradation

Furan formation from amino acids is studied in carbon-13 labelling research and observed to formed acetaldehyde and glycolaldehyde, which are then formed furan after aldo condensation and cyclization process. Formation of these intermediates, acetaldehyde and glycolaldehyde highly depends on the type of amino acid [33]. Serine and cysteine are known to follow two pathways, Strecker reaction or decarboxylation. Strecker reaction produces glycolaldehyde and decarboxylation produce acetaldehyde [35]. Both of these amino acids do not require sugar molecules and go through aldo condensation and produce aldotetrose derivatives, which after the cyclization process produce furan. Many amino acids, for example, aspartic acid, threonine and a-alanine do not form furan after direct metabolism but produce acetaldehyde only. These amino acids further require reducing sugars to produce glycolaldehyde and then furan as the end product. Figure 12.3 shows furan formation via amino acids.

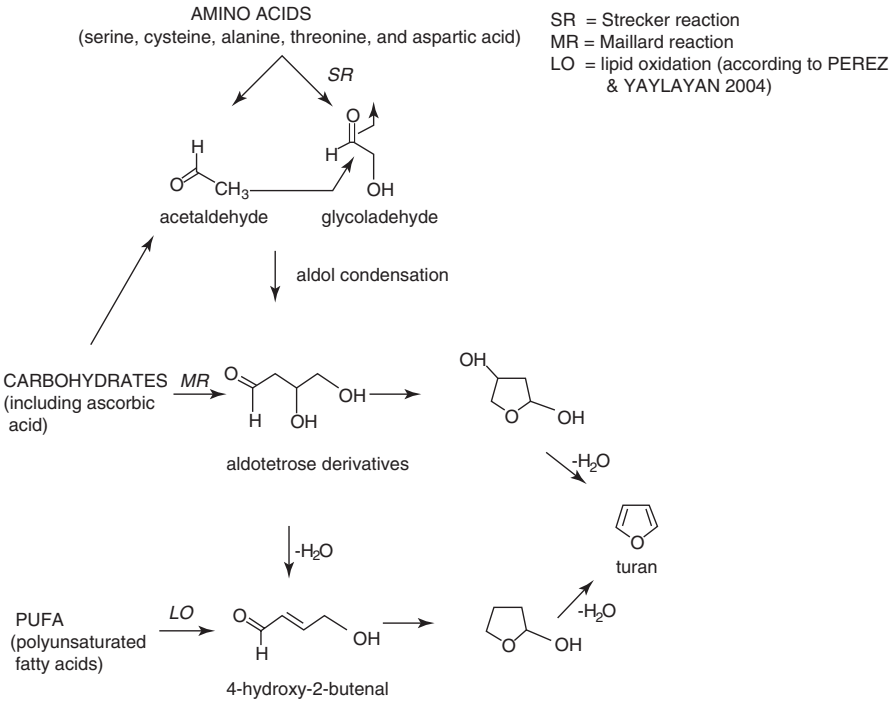


Fig. 12.3 Suggested parent furan formation pathways from three major sources, i.e., amino acids, carbohydrates, and fatty acids

Furan Formation via Ascorbic Acids Oxidation

Another precursor of furan formation is ascorbic acid which go under oxidation reaction. It acts like reducing sugars and follow two parallel methods to form furan [34]. Ascorbic acid will go either under aerobic condition or anaerobic condition which ultimately produce furan but follow two different ways. In aerobic condition, it oxidized to produce dehydro-ascorbic acid in the presence of the acidic environment. Which further hydrolysed and form 2,3-diketogulonic acid (DKG), which further undergo chemical reaction to produce xylosone and 2-deoxy-aldotetrose by decarboxylization. These two compounds are then used to form furan. In anaerobic condition, dehydro-ascorbic acid cannot be produced therefore ascorbic acid is unable to oxidized to produce DKG. Therefore, it goes to hydrolyzation and b-elimination, which further undergoes decarboxylation and produce 3-deoxypentosulose (DP). This 3-deoxypetosulose when undergo further processed formed ribose that is used in furan formation. Ascorbic acid is also responsible to produce furan derivatives such as furfural and furoic acid in the presence of high temperature at 300 °C and the absence of water. Ascorbic acid-producing furan and derivatives gain its attention as it has impact on browning reaction occur in orange juice along with other compounds. Research has shown it produces furan or its precursors, that react with sugars and chelating agents. Figure 12.4 shows furan formation via ascorbic acids.

Furan Formation via Oxidation of PUFA and Carotenoids

Oxidative degradation of polyunsaturated fatty acids (PUFAs) in food processing produce lipid peroxides. This lipid peroxides cause undesirable flavour in food. As an intermediate of this reaction 2-alkenals, 4-oxo2-alkenals and

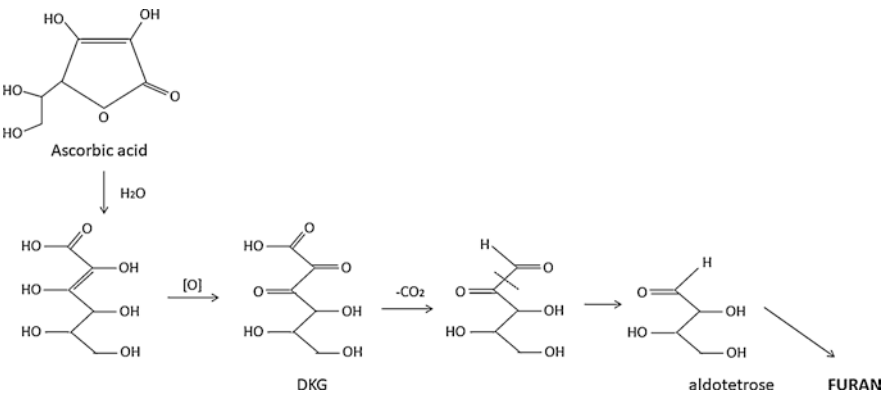


Fig. 12.4 Formation of furan through Ascorbic acid

4-hydroxy-2-alkenals are formed, of which 4-hydroxy-2-alkenals is a known precursor for furan formation [36]. Study on monounsaturated fatty acid, for example, oleic acid, show no furan is produced. While linoleic acid and linolenic acid produce furan, measured as 125 and 625 ng/g, respectively. The reaction was carried out at 118 °C for 30 min and concluded that linolenic acid required a lower temperature to form furan from that of ascorbic acid or Maillard reaction [37]. Fatty acids containing furan rings actively search for radical to react and form dioxoenoic fatty acids. These dioxoenoic fatty acids are highly unstable and cannot exist on their own, therefore react with thiol, in particular cysteine or glutathione and form thioethers [38]. They trap specifically hydroxyl radicals as powerful antioxidants and this is regarded as their main function in different biological systems [39]. They also inhibit red blood cell haemolysis caused by singlet oxygen (disintegration of RBCs) [38].

Furan Formation Through Degradation of Carbohydrates

Furan is detected to be formed in large number in food processing as a result of non-enzymatic browning reaction as well as Maillard reaction using carbohydrate as precursors. In the presence of amino acids Maillard reaction took place and produce intermediates 1-deoxy- and 3-deoxyosones, 2-deoxy-3-keto-aldotetrose and aldotetrose by reduction of hexoses [33]. Some studies suggested 2-deoxy-aldotetrose and aldotetrose as furan precursor because furan is easily formed by aldotetrose. Furan is also produced from pentose sugar in the presence of amino acids, the reaction of pentose sugar, for instance, ribose leads to the formation of intermediate 2-deoxyaldotetrose, a precursor of furan. Furan formation from carbohydrates via thermal degradation is a complex process and it involves many pathways but mostly involve Maillard reaction.

In the absence of amino acid furan in formed from intact sugar skeleton. In this process of furan formation formic acid and acetic acid are formed as by-products as a result of sugar degradation. In this case aldotetrose is also formed to a lesser extent by retro-aldol cleavage [40]. In this degradation process aldotetrose derivatives produced as intermediate, which go to cyclisation process to produce furan [33]. Pathway A and D explains furan formation process in presence of amino acids, whereas pathway B illustrates the furan formation in absence of amino acids. Furan is eventually formed from all aldotetrose derivatives [33]. The parent furan may also be produced by pentose sugars such as ribose in the proximity of amino acids. Similar to pentose rings, hexoses can be transformed into their 3-deoxyosone derivative products via reaction of amino acid or by dehydration in the hydroxyl group C-3 [41]. The resultant intermediate may endure α-dicarbonyl cleavage to generate 2-deoxyaldotetrose, a direct furan precursor.

Furan Detection Methods

Furan detection in food was a critical method as its toxic nature present the idea that its presence in food could be potential threats to health. For its detection FDA first incorporated a technique to quantify its presence in food. The sample is prepared in cold conditions and done the headspace analysis at 80 °C. For separation of furan porous layer open tubular (PLOT) columns are used for chromatographic separation along with mass spectrometric detection in selected ion monitoring mode. In this method, bounded polystyrene-divinylbenezene in a column is used to separate small volatile molecules. Furan was quantified using standard addition method by using deuterated furan internal standard.

Headspace Analysis

Furan is separated from the food sample using headspace techniques. In this method, magnetic bars are added to headspace vial and effective separation is done depending on equilibration time, and efficient agitation, liquidity of sample and temperature [42]. To make the sample fluid, a sufficient amount of water is also added. Although the headspace method requires to heat the sample so analytes are volatilized to headspace but in case of furan heating is not suggested because of its highly volatile nature. A few studies reported to increase the temperature from 30 to 50 °C to increase the efficiency but rather increasing the temperature it is suggested to increase the salt. Instead of high temperature, many studies concluded that appropriate temperature for furan detection is 50 °C or below [43].

Headspace Sampling by Solid Phase Microextraction (SPME)

For effective analysis, headspace sampling phase microextraction method is preferred over the headspace method. In SPME a needle is used, which has polymeric material coated on its tip. This SPME needle is subject to the headspace of a vial in which analytes are present. After 10–60 min of exposure, the analytes are filtered out with the help of polymeric material at the tip of the needle. Then it is desorbed by heating from 90 to 300 °C for 15 min and injected into GC column. In headspace, it is injected directly into the Gas Chromatography Spectrometry System. SPME is a more sensitive method because it allows the concentration of sample material. Optimal conditions for SPME are depended on many factors such as time, temperature, fibre type, aqueous phase saturation and extraction in headspace vial. To determine the best possible fibre many researches have been conducted and caboxen/polydimethylsiloxane is concluded to be more effective, followed by divinylbenzene/carboxen/polydimethylsiloxane regarded as next best option. Optimization

conditions for fibre exposure time and temperature for furan are reported to be 50 °C or less to avoid the additional furan formation. Although the time of exposure is not having a remarkable effect for furan analysis purpose 20 min are chosen.

Identification and Quantification of Furan Using GCMS

Furan can be identified in GCMS by means of several methods. One of this methods is measuring GC retention time and another way to quantify is by comparing the quantity of furan ion at m/z 68 with a qualification of ion at m/z 39. This ratio is measured and again compare it to the ratio of furan ions with standards. In quantification several standards are measured, using d4-fuan as labelled internal standard.

Furan Quantity in Food

Furan in food production has been well documented and found in not only commercially prepared but homemade food as well [8]. Furan is associated with flavour in food. The highest level of furan has been found in coffee [6]. Furan in food products has become a concern for many health agencies due to their toxic nature. The toxicity of furan has been studied in many animals and confirmed its toxicity, for instance, it has been tested on rats and target the liver, which is the main target of furan toxicity [11]. Due to its health causing issues many authorities such as US Food Drug Administration (FDA), European food safety Authority (EFSA), International Agency for Research on Cancer (IARC) classified furan as toxic substance related to cause carcinogenicity in human beings. Firstly, the US FDA analysed the amount of furan present in foods such as commercial canned and jars in 2004 (Table 12.2). And afterwards other authorities also tested furan quantity in different foods. EFSA and food standards agency (FSA) monitored furan level in foods (Table 12.3) [44].

Metabolism of Furan

Furan metabolism was tested in rat where rats were subject to furan dosage and analyse all elimination routes, like urine, air and faeces, for furan metabolites. In first 24 h approximately 80% of furan was recorded to be eliminated via urinary and air [45]. The researchers hypothesized that after the furan opening of the oxidative ring, the carbon dioxide was formed. Although there was no clear evidence at the time, the researchers proposed that 2- and 3-methylfuran would be identical [46]. Furan itself transformed into a reactive intermediate *cis*-but-2-ene-1,4-dialdehyde BDA, which subsequently confirmed in experiments using a trapping agent for rat

Table 12.2 Furan quantity detected by FDA in different products

Product	Furan (ng/g)
Baked goods	
Archway ginger snaps	5.6
"Jiffy" corn muffin mix	ND
Bagel nation plain bagels (toasted)	ND
Biscuit shack restaurant biscuits	ND
Bodacious bagels plain bagels (toasted)	ND
Bodacious bagels whole wheat bagels (toasted)	ND
Dunkin' donuts french cruller doughnuts	3.6
Nabisco fig newtons	1.7
Newman's own organics	12.5
Nabisco Lonsa Donne shortbread cookies	3.6
TOPS ginger snaps	30.1
Fig newmans	12.5
Whole foods blueberry muffins	ND
Foods morning glory muffins	ND
Beverages	
Celestial seasonings 100% green tea bags	0.4
Dominick's 100% orange juice (canned)	1.4
Gold peak tea lemon iced tea	0.8
Lipton summer peach ice tea mix	ND
Lipton unsweetened pureleaf iced tea	0.4
Mountain dew live wire	1
Nestea unsweetened ice tea mix	ND
Safeway green tea 100% natural tea	0.5
Sunkist orange soda	0.4
Breakfast cereals	
B&G cream of wheat enriched farina	ND
Food lion raisin bran	13.8
Great value oven-toasted old-fashioned oats	ND
Harris teeter bran flakes	16.1
Harris teeter frosted fruito's	6.1
Heartland granola cereal ND	ND
Kellogg's all-bran complete wheat flakes 25.4	25.4
Kellogg's fruit loops 15	15
Nabisco cream of wheat ND	ND
Post grape-nuts 11.6	11.6
Post raisin bran 15	15
Post shredded wheat 2.3	2.3

(continued)

Table 12.2 (continued)

Product	Furan (ng/g)
Infant food	
Beech-nut mixed cereal for baby	3.9
Earth's best organic whole grain rice cereal	ND
Gerber graduates biter biscuits	6.4
Gerber prunes with apples	10.1
Gerber single grain barley cereal for baby	ND
Gerber single grain rice cereal for baby	ND
O Organics for baby organic prunes 11.6	
Mixtures	
Flavorite Worcestershire sauce	14.1
French's Worcestershire sauce	14.9
Hunt's bold barbecue sauce	15.5
Kraft honey hickory smoke barbecue sauce	13.5
Open pit original barbecue sauce	28
Snacks	
Alpine valley butter flavor popcorn	28.5
Anderson's frozen custard curly que. fries	ND
Arby's curly fries	ND
Bachman thin'n right baked pretzels	62.8
Cape cod old-fashioned kettle cooked potato chips	3.5
Doritos Nacho cheese flavoured tortilla chips	12
McDonald's french fries	ND
Rold gold classic style sticks pretzels	40.1
Ruffles original baked! potato crisps	21.7
TOPS festingos round bite size 100% white corn tortilla chips	5.8
TOPS pretzelwerks snaps pretzels	37.9
Tostitos 100% white corn crispy rounds	6.2
Troyer farms premium popcorn with white cheddar cheese	30

Table 12.3 Furan detection by EFSA in 2004 [44]

Product	Furan (ng/g)	Sample
Coffee instant	394	109
Coffee roasted ground	1936	110
Coffee roasted bean	3660	30
Coffee brew	42–45	89
Baby food	31–32	1617
Infant formula	0.2–3.2	11
Baked beans	57	22–24
Beer	3.3–5.2	102
Cereal product	15–18	190
Fruit juice	2.2–4.6	250
Fruits	2–6.4	142
Milk product	5–5.6	64
Sauces	8.3–11	271
Soups	23–24	270
Vegetables juice	2.9–9	80
Cocoa	9–10	14
Snacks and crisps	9.6–10	133
Tea	1–1.7	22
Wine and liquors	1.3	20
Vegetable fats	1.5–1.7	13
Soy sauce	27	94
Soya products	6.7	15
Meat product	13–17	174

liver microsomes. There was no evidence for an epoxy formation, which indicate that if intermediate plays a role, it must be of short duration [47].

Metabolism of Methyl Furans

It has been demonstrated that 2-and 3-methylfuran can be bioactivated in reactive species by rat lung and liver microsomes [46]. In 2-methylfuran 3-acetylacrolein(=4-oxopent-2-enal) were recognized as reactive metabolite, whereas in 3-methylfuran reactive metabolites were 2-methylbut-2-enedial, identified using semicarbazide as trapping agent. Studies of 2-methylfuran [48] have shown that it can also be bioactivated by kidney microsomes. To verify 2-methylfuran as inhibitor for cytochrome P450(CYP), a study conducted in which 3-Acetylacrolein is used. High reactivity of microsomal protein in presence of 3-acetylacrolein and strong inhibition of 2-methylfuran has been confirmed and indicate that 2-methylfuran act as suicide substrate. After pre-treatment with piperonyl butoxide and phenobarbital partial inhibition of 2-methylfuran metabolism was observed but pre-treatment with *N*-octylimidazole it was inhibited completely [48]. 2-methylfuran does not interact directly with

glutathione (GSH) in aqueous incubate [49]. Partial reduction of GSH is caused by 2-methylfuran in haemolysates. For this depletion of GSH, 2-methylfuran must be co-incubated with microsomal bioactivating system. This indicates that bioactivation of 2-methylfuran is required, which is available in erythrocyte cytosol or in microsomal system. It can be inferred from previous knowledge of biotransformation that alkylfurans can also be oxidized at the sidechain to allow furyl alcohols to grow and oxidize to create the required acids and aldehydes. These additional metabolism routes and their effects on substances toxicity have not been studied.

Furan Biotransformation Enzymes

The main contributor to the metabolism of furans is CYP2E1 [50]. A study indicates correlation between *p*-nitrophenol (CYP2E1 substrate) conversion and furan metabolism in human microsomal incubations. Among all CYPs the highest activity was observed in CYP2E1, at least 5–10 times greater than other forms. For numerous other CYPs types minimal catalytic activity was observed [51]. Alizadeh et al. [50] demonstrated that CYP-catalysed biotransformation of furan results in inactivation of CYPs and that CYP2E1 is more heavily affected than other CYPs. From metabolism studies with 2-methylfuran with inducers and inhibitors of CYP2E1 [48], it may be anticipated that also this alkylated furan and possibly also 3-methylfuran are metabolized predominantly by CYP2E1, but contrary to furan, studies with purified CYP enzymes are not available for these two alkyl furans. Therefore, there is no direct evidence for an involvement of CYP2E1 in the biotransformation of 2- and 3-methylfuran. Reports of CYP2E1 metabolism with 2-methylphuran inducers and inhibitors [48] may also predict that CYP2E1 is also the primary metabolism of this furan alkylated, probably even3-methylfuran, however, unlike furan, reports of these two alkyl furans are not possible with pure CYP enzymes. There is therefore no direct evidence for the CYP2E1's role in 2-and3-methylfuran biotransformation.

Risks of Furan to Digestive Track and Enzymes

Furan mainly target liver and cause toxic and carcinogenic effects [12]. Due to high ability of cytP2E1 furan is bioactivated into a reactive intermediate BDA. Hepatocellular changes and disruption to the epithelium of bile duct which can result in cholangio fibrosis and the further production of cholangio carcinomas could be attributed to the hepatotoxicity impact of furan [52]. Major elimination route for furan removal is bialiary excretion [45]. As a consequence, prolonged exposure to furan metabolites toxicity in the bile duct results in damage to the epithelium layer of bile duct [7]. The caudate lobes and left subcapsular surface of liver are highly exposed to furan toxic effects including fibrosis, inflammation and

necrosis [11, 53]. For this differential liver lobes susceptibility to furan, three likely explanations have been suggested [11]. One explanation is caudate liver lobe allows portal venous circulation; therefore, it show higher exposure as compared to left, right and median lobes [11]. Another explanation is, there are intrahepatic lobe variations, in furan metabolism [54] and lastly, as left or caudated liver lobes are next to the stomach, therefore raising the risk of direct furan spreading through the stomach [11].

Biochemical parameter of serum is usually evaluated for toxicology and liver damage assessment prior to histopathology confirmation [55]. Many enzymes present in liver such as serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) are conjugated to bilirubin. Bilirubin is released into the circulation after the cell damage [56], which make them most sensitive biomarkers for any liver injury [11]. Among them, ALT is consider to be most specific enzyme for hepatocyte damage evaluation [13]. Moser et al. illustrated in an animal study that mice treated with 1, 2, 4, and 8 mg/kg body weight furan increased dose-dependent levels of ALT, with evidence of hepatotoxicity at even lower concentrations. Enhanced hepatocarcinogenesis in doses above 4.0 mg/kg body weight was also noticed [13]. In another test, in mice with both sexes at 8 mg / kg furan body weight, Gill et al. showed a significant improvement in ALT function. The behaviours of ALP and AST in male and female rats were both consistent in this experiment [11]. After administration of furan through nasogastric gavage for 90 days at different doses to rats previously treated with furan, improvements in enzyme activity, elevated conjugated and total bilirubin levels are observed [11]. Increases in overall bilirubin that result from cholestasis following intrahepatic or extrahepatic bile flow deficiency induced by the release of enzymes attached to the hepatic membrane [11, 53].

Furan and its derivatives effect on digestive system including effect on liver, proposed that after exposure of furan these tissues undergo to high risk [57]. Some opposing results can also be observed due to many factors as exposure times, animal age and furan dose [58]. Gamma glutamyltranspeptidase (GGT or γ-GT), a plasma membrane enzyme, [59] level increases in many diseases such as liver and cardiovascular disorders and diabetes mellitus [60]. Therefore, rendering it a reliable marker for diseases detection. Some drugs and alcohol are also responsible for higher level of GGT in cell and tissues. Furthermore, there is evidence that cell resistance during oxidative stress is increased due to increase in GGT expression, which is responsible for GSH synthesis that boosts the cell resistance. Increased GGT level plays crucial role in oxidative stress regulation [61]. A correlation has been studied between hepatic steatosis and plasma GGT [62]. In older people higher serum GGT level is suggested to be associated with liver and cardiovascular diseases [62]. Its higher level, out of normal range also serves as biomarker for atherosclerosis [63]. A direct and strong correlation between GGT level and urinary furan has been determined in a cross-sectional study. Though animals and in vitro experiments are subject to higher furan dose as compared to what human are exposed to naturally. But this experiment results concluded that the amount of furan received by human can also be destructive to tissues and oxidative reaction [64].

Dyslipidemia may be another furan toxicity risk. Liver is an important source of lipid metabolism and plays a crucial part in serum protein synthesis. Chronic liver disorders decrease the biosynthetic efficacy and ability of the liver and subsequently decrease the triglyceride, cholesterol and HDL-C levels [65]. To identify the hepatic functions and liver diseases these indicators such as total protein, triglyceride, albumin, cholesterol and glucose can be used as detection marker from medical point of view. Therefore, it can also indicate catastrophic effect on lipids, protein and glucose synthesis in liver due to furan toxicity [58].

Changes in serum proteins, glucose, cholesterol and triglyceride most likely determine general metabolic changes in contrast to toxic effect on specific organs [56]. It should be remembered that there is no specific understanding of the precise mechanisms involved in these changes. However, inhibition of enzymes involved in TCA cycle, after exposure to furan, has been indicated via metabolomics analysis [64]. On the other hand, to compensate for the lack of carbohydrate products, the use of fatty acids as an energy source is increased. This phenomenon may lead to a significant reduction in serum TG concentrations. In fact, there may be a significant increase in different amounts of amino acids due to proteolysis from liver damage or use of proteins as a source of energy [64]. The mechanism of these changes is explained in further studies. Another section of the digestive system that may be affected by furan is exocrine pancreas. Serum amylase is a major gastroenteric enzyme and is a key indicator of the function of the pancreas [66]. Gavage-based administration of furan to Fischer-344 rats and mice caused serum amylase increase at different concentrations [11]. Some studies, however, suggest that in animals with liver and infectious diseases, amylase could be reduced [67]. Various animal studies exhibit the effects of furan on the digestive system (Table 12.4). Many mechanisms are proposed at the cellular level to explain the reasons for the destructive effects of the furan and its active metabolite, BDA, particularly in hepatic cells called cytolethality.

Toxicity of Food Contaminant Furan on Liver and Kidney of Growing Male Rats

Furan is reported in mice and rats as carcinogenic and can also be carcinogenic in humans [72]. Due to high prevalence of hepatocarcinogenic lesions and carcinomas recorded in mice it is also considered to be possible hepatocarcinogenic in humans [69]. CYP2E1 metabolizes furan and transforms it into a cytotoxic metabolite named, *cis*-2-butene-1,4-dialdehyde. It then attaches on proteins and nucleotides irreversibly [6]. The furans toxicity is reported to be linked to cis-2-butene-1,4-dialdehyde metabolite [73]. Furan metabolites also cause toxic effects by influencing cell proliferation and dissociation of mitochondrial oxidative phosphorylation [74]. Furan's acute impact has not been studied sufficiently, but still chronic low level is considered to be cancer-related [75]. In the National Toxicology Program

Table 12.4 Summary of studies regarding furan in digestive system

Design	Duration	Dose of furan	Results	References
Animal study (Rat)	90 days	30 mg/kg body weight	100% incidence of cholangiocarcinoma	Maronpotet al. [68]
Animal study (Rat)	24 months	0, 0.8, 1.5, 2, 4 and 8 mg/kg body weight	Oral administration of furan in all doses tested and results showed numerous non-neoplastic hepatic lesions including bile duct hyperplasia, cholangiofibrosis, necrosis, chronic inflammation, bialiary cell proliferation and nodular hyperplasia of hepatocytes with dose-dependent increasing severity	Program [69]
Human study (cross-sectional)	_	_	GGT level was strongly correlated with the urinary furan concentration	Jun [70]
Animal study (Rat)	90 days	8 mg/kg body weight	100% incidence of Hyperplasia, Cholangiofibrosis, Basophilia, Anisokaryosis and Pigmentation	Gill et al. [11]
Animal study (Rat)	28 days	0, 0.1, 0.5, and 2 mg/kg body weight	there was no significant change in plasma ALP, AST and ALT	Mally et al. [57]
Animal study (mouse)	3–6 weeks	15 mg/kg body weight	Serum ALT was significantly increased	Terrell et al. [53]
Animal study (Rat)	3–24 months	0.92, 2 and 8 mg/kg body weight	Furan exposure induces irreversible down-regulation of miR-375 in rats epigenetically	de Conti et al. [71]

study, furan was mixed in corn oil and administered to B6C3F1 mice and F-344 rats to both sexes. In 2 years analysis 8 and 15 mg/kg/day dose was applied to B6C3F1 mice and 2,4 and 8 mg/kg/day dose was applied to F-344 rats and results showed sufficient increase in hepatocellular adenomas and carcinomas [69]. Furan genotoxicity were studied in V79-Mz and V79-hCYP2E1-hSULT1A1 cells and treated with 3–16 μM furan. The results indicate exchange of sister chromatin and induce genotoxicity. Furthermore, furan study at low dose (2, 4, 8 and 15 mg/kg/day), when administered to mice for 4 days, resulted in insignificant increase in micronucleated cells [74]. The liver damage can be assessed by serum biochemical parameters because liver is sensitive to many chemicals due to its anatomical proximity to blood supply from digestive tract and also due to its role in concentration and biotransformation of chemicals [55]. Many chemicals also target kidneys, therefore for

furan toxicity in healthy men and women [70] assessed levels of urinary furan and γ-glutamyltranspeptidase in normal diets. Their findings depicted a relationship between the rate of γ-glutamyltranspeptidase and the number of urinary furans. Two dietary furans named furfuryl alcohol (FA) and 2-furyl methyl ketone (2FMK) were administered to Swiss albino mice for 60 and 90 days. The dose of two compounds was 2000 and 4000 ppm and results indicated focal necrosis, pycnosis and vacuolation by FA in liver and tubular epithelium damage in kidney. There was no significant damage in liver and kidney from the 2-FMK [76].

Protective Effects of Apigenin Against Furan-Induced Toxicity in Mice

Furan toxicity has been reported in many studies and due to its adverse effects on human health it gains attention to search for mitigation of its impact [77]. A few natural compounds have been found that can reduce the toxic effect and has been studied in mouse model. It has been reported the impact on reduction of toxic effect of furan by apigenin [78]. Apigenin is naturally found in many fruits and vegetables and tea. They did experiments for effect of apigenin in mouse model for reactive oxygene species (ROS), oxidative damage in liver and kidney and cytokines. Firstly, the ROS was increased by applying furan alone and mice showed higher level of ROS. When these mice were subsequently treated with apigenin the level of ROS decrease with increase of concentration of apigenin, ranging from 5 to 20 mg/kg per day.

The effect on liver and kidney by furan was tested by GSH. GST, SOD, MPO and MDA levels. When treated with furan GSH, GST and SOD levels were reduced significantly in liver and kidneys. These mice with reduced GSH were then treated with apigenin and enhanced level of GSH was observed as 5, 10, and 20 mg/kg/day. Similarly, GST activities were enhanced by 45% in liver and 78% in kidneys and SOD activities were enhanced by 114.5% and 108.4% in liver and kidneys, respectively. On the other hand, MPO and MDA levels were increased when treated with furan and when doses of apigenin were administered to mouse, the activities of MPO and MDA were decreased [78].

Furan-Induced Cardiotoxicity in Diabetic Rats and Protective Role of Lycopene

Diabetes mellitus (DM) is a condition that causes high blood glucose level in human and is variable in this process. The major medical issues were DM and its complications. For DM patient, to decrease heart damage potential sugar levels in blood should be under control [79]. In a desirable timeframe in DM, this has made progress. Even in such cases, heart damage and cardiovascular disorders are still

responsible for high mortality-related DM levels [80]. Most of the biological problems like: oxidative damage, cardiac dysfunctions that suggest their effects with problems caused by DM. Several evaluations clarify that some applications can impede the development of DM [81, 82].

In some of studies [83, 84] scientists found that diabetes has impaired the level of MDA and many organs' antioxidant defence system. Chemicals that treat animals and humans may create oxidative stress in cells caused by LPO. Furan induces in living things undesirable effects [12]. Another study found that the antioxidant defence system was affected by furan [58]. MDA, which is the LPO predictor, has been assessed and the damage has been calculated in this analysis. It was shown in another study that furan increased production of ROS, induced development of LPO, and generated oxidative stress [85]. Several studies suggest that diabetes can cause damage to many tissues [83].

Previous studies have shown that DM has modified the function of antioxidant enzymes [83, 84]. Amid chemical treatments, reductions in antioxidant enzyme activity were also seen. There is a lot of evidence that biochemical disruption and physiological disfunction induce furan application to living organisms [12]. The U.S. user's median furan intake is about 0.25 μg/kg body weight (bw)/day [86]. But for ever, people will be subject to this dosage. In this analysis, this dosage is expanded to see the results of a subchronic examination of furan aggregation over the years. It has also been found that the behaviours of antioxidants in rats feeding on furan were shown to change. Increases in enzyme activity can be caused by ROS production [87]. Cardiotoxic effects of furan and lycopene have also been tested in diabetic rats and conducted on five different experimental groups of rats for 28 days [88]. They divided experimental rats as control, diabetic control, diabetic lycopene, diabetic furan and diabetic furan plus lycopene. The results were evaluated as level of MDA and antioxidant, SOD, CAT, GST, GPx. In diabetic rats' level of MDA was high as compared to control group. Diabetic group treated with furan had shown considerable increase in MDA levels. The decrease in antioxidant enzymes was observed in both groups as treated and untreated diabetic groups. While treated with furan significant decrease was observed as compared to diabetic control group. The heart section of furan treated rats was examined and found pathological alterations, oedema in connective tissue and degenerative changes. It was previously studied that changes in lipid and glucose metabolism and antioxidant enzymes modification cause hyperglycaemia in diabetic patients [89]. DM also responsible for alteration in antioxidant activities [83, 84].

Furan Efficiently Rescue Brain Cells from Cell Death Induced by Oxidative Stress

Many neurodegenerative, diabetes, ageing and heart disorders can be caused by reactive oxygen species (ROS), free radicals and peroxides, that are due to oxidative stress in cells. Oxidative stress in cells that give rise to reactive oxygen species

(ROS), peroxides and free radicals are found to be involved in a wide range of pathological disorders such as neurodegeneration, ageing [90], heart disease and diabetes [91, 92]. Nervous system, especially brain tissues are vulnerable to oxidative stress, this is because of prevalence of highly unsaturated fatty acids and high metabolic turnover [93]. ROS has gained attention in functional food science and methods has been developed for protection against ROS in health and nutrition for many years [94]. While there is growing evidence that regulation of oxidative processes is necessary to control dangerous outcomes [95]. It is difficult to search for substances that interact with ROS efficiently in situ. Many antioxidants like Vitamin E can be effective against oxidative stress but also induce apoptosis. Therefore anti-apoptosis drugs have gained attention to prevent neurodegenerative diseases [96]. Furan fatty acids may be used as radical scavengers in lipid peroxidation process [97]. In addition, furanoids [98] were studied to inhibit b-amyloid aggregation, while the anti-inflammatory activity of furan derivatives by COX-2 inhibition was identified [99]. Furan as anti-apoptosis has been studied on C6 cell line of rat brain. It was already determined that C6 cells are important in defensive mechanism and responsive to injuries [100]. When these cells were exposed to furan fatty acids F6 (12,15-eposy-13,14-dimethyleicosa 12,14-dienoic acid), it is observed to protect cell death due to oxidative stress.

Furan Metabolite Is Elevated in Diabetes and Induces β-Cell Dysfunction

Gestational diabetes mellitus (GDM) is a condition of resistance of insulin despite no prior history of glucose intolerance in pregnant women and developed diabetes during late pregnancy [101]. The cause of GDM is said to be significant decline in b cells function, as these are not adapted to high metabolic demands [102]. Although many studies have showed relationship between type 2 diabetes T2D and b cells, and suggested that for development of diabetes developments metabolites may be involved. GDM progresses to T2D and experiments were conducted to scree plasma for identification of GDM causing factors. Metabolomics study of plasma revealed that furan fatty acids metabolite 2-carboxy-4-methyl-5-propyl-2furanpropamoic acid (CMPF) were raised in human plasma with GDM conditions and also cause glucose tolerance [103].

Prevention and Removal Strategies of Furan from Food

As toxic substance, it was advised to mitigate furan harmful effects and for that purpose two major approaches are used.

Prevention of Formation of Furan

During food processing many strategies can be adopted to prevent its formation and removal after formation. As a preventive measure thermal input reduction process is used. In this approach decreasing the heat in industrial process can be effective to mitigate furan, as furan needs heat for its formation [104]. The reduction in thermal reduction can be obtained by applying low pressure and temperature for long time or by setting the oven at high temperature initially and decrease it afterwards. Another way to obtain low thermal reduction is through dielectric heating. Another preventive measure can be used in formulation process is the use of competing ingredient or inhibitor to slow down the formation rate and precursor concentration [34, 105].

Removal of Furan After Formation

A postprocess method called vacuum technology is proposed to remove furan, by proper application of temperature, time and pressure according to their chemical and physical properties. A finished product undergoes to vacuum treatment where undesired molecules are removed. But this vacuum treatment efficacy is dependent on many variables such as food composition, water content and nature of molecules [106]. To remove furan and 5-hydroxymethylfurfural (HMF) hydration step is needed before vacuum step. A study conducted on furan removal through vacuum steps showed significant decrease in furfuryl, furfuryl acetate and 5-methylfurfural from coffee at pressure 2.7 kPa and temperature 60 °C for 3 min [107].

Conclusion

Furan is found in environment abundantly in many products like processed food, industrial product, pharmaceutical product and environment component. The increasing amount of furan in environment has become a potential compound for health concerns. Although direct evidences and information of its effects on human are limited. But many studies particularly conducted on model animals determine it toxicity. Furthermore, it was studied that furan is mostly eliminated from body after metabolism and only a small amount has been remained. But amount of furan harmful for health is not yet been determined. Though it is said a small amount can be injurious. Furan is also known to be absorbed by intestine and lungs and can easily pass through membranes, therefore can affect different body parts. However, to mitigate its effect is yet a challenge and many processes like pasteurization and sterilization cannot be effective. A few compounds are tested to reverse furan effects and few industrial processes is studied to compensate the effects, but these are not implemented at large level yet.

Conflict of Interest All the authors have no conflict of interest.

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Chapter 13
Role of Heavy Metals in Metabolic Disorders

Kanwal Irshad, Kanwal Rehman, Fareeha Fiayyaz, Hina Sharif, Ghulam Murtaza, Shagufta Kamal, and Muhammad Sajid Hamid Akash

Abstract The majority of the heavy metals are considered toxic to the human beings by interfering with the normal functions that are taking place in the human body by disrupting metabolic processes and their exposure may be due to natural or anthropogenic sources. Heavy metals act as endocrine-disrupting chemicals (EDCs) by disrupting the mechanism of action of endogenous substances. Heavy metals such as cadmium and arsenic have a negative impact on some enzymes that are involved in carbohydrates and lipids metabolism and lead to an abnormal level of glucose and lipid, cholesterol, and triglycerides. This is responsible for inducing the pathogenesis associated with diabetes mellitus and insulin resistance. These metals are also responsible to induce reactive oxygen species and suppress antioxidant defense mechanism. The stress-induced by oxidation is highly linked with metabolic syndrome. These conditions lead to a risk of diabetes-associated cardiovascular diseases. While on the other side, some of the heavy metals notably zinc which is

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considered as an essential nutrient, play its significant role in metabolic disorders by suppressing oxidant effect, reducing obesity and lipogenesis. In this chapter, we have briefly overviewed the role of heavy metals that act as EDCs in metabolic disorder via interfering various transcriptional and metabolic pathways while the other heavy metals which have a beneficial role in the amelioration of metabolic disorders.

Keywords Heavy metals · Carbohydrate metabolism · Lipid metabolism · Oxidative stress

Introduction

Endocrine-disrupting chemicals (EDCs) can be defined as exogenous substances or mixtures of substances that interact in any way with endogenous hormonal signaling, not only affecting the production, secretion, and transportation of hormones but also has an effect on their cellular metabolism, binding action and elimination [1]. EDCs play a crucial role in obesity, diabetes, and cardiovascular system. In case when EDCs act as obesogens, they show their effect on adipocyte tissues and also on the brain for induction of obesity which causes glucose intolerance, insulin resistance, dyslipidemia and enhanced expression susceptibility towards cardiovascular disorders and type 2 diabetes mellitus. In case when EDCs act as diabetogenic, they have a direct effect on the islet of Langerhans due to which insulin synthesis and release may be increased or decreased, as a result, may be hyperglycemia or hypoglycemia occur. Due to the impairment of insulin signaling and insulin resistance, the metabolic syndrome occurs. Some EDCs also have a direct effect on the heart and cause cardiovascular diseases [1]. EDCs are basically chemical substances which exhibit agonist and antagonist effect on the endocrine system. Many heavy metals such as lead, cadmium, mercury, nickel, and arsenic have endocrine-disrupting activities [2].

Heavy metals are considered as a broad class of metals and metalloids having a relatively high density and are very toxic in nature even at parts per billion levels. Examples include lead, arsenic, mercury, cadmium, zinc, silver, copper, iron, chromium, nickel, palladium, and platinum. Both natural and anthropogenic sources such as mining, automobiles exhaust, and industrial discharge are major sources of releasing these metals into the environment [3]. Heavy metals in the form of oxides and sulfides ore naturally occur in the earth's crust and rocks. Heavy metals can be halted out in the form of minerals from many different types of ores such as sulfides of cobalt, lead, cadmium, mercury, iron, and arsenic. The leaching of heavy metals may occur due to naturally occurring mechanisms such as weathering of rocks, mining, and volcanic eruptions processes. Leaching of heavy metals into oceans, rivers, and lakes can cause pollution and affects its surrounding environment by acidic rain

[4]. Heavy metals can also cause environmental pollution due to metal corrosion, deposition of metals in the atmosphere, leaching of heavy metals, soil erosion of heavy metals and metallic ions, re-suspension of sediments, and evaporation of metals from water reservoirs to soil and groundwater [5]. These heavy metals can accumulate in the human body by different processes and cause harmful effects on them. These heavy metals have the ability to bind with macromolecules and alter their normal cellular functions. It may lead to many adverse effects on the health of humans by affecting their central nervous system, lungs, liver, and kidney [6]. In the proceeding sections, we have briefly summarized the role of most important heaving metals that act as EDCs in metabolic disorders.

Cadmium

Sources and Exposure

Cadmium is a heavy metal that naturally occurs in ores. It generally acts as a stabilizer in many products such as polyvinyl chloride containing products, many alloys, and color pigments. Phosphate fertilizers are also a major source of cadmium exposure [7]. The activities in the environment such as the burning of fossil fuels, electroplating phenomena, usage and production of pigments and batteries containing alkaline nickel-cadmium and welding have more contribution to acting as a source of cadmium as compared to naturally occurring process in the environment. The naturally occurring processes such as volcanic activity, forest fires, erosion of soil, and weathering of rocks are major sources for releasing cadmium into the environment [8]. The human being may be exposed to cadmium in several ways (Fig. 13.1). Mining and smelting of non-ferrous metals and synthesis of compounds containing cadmium are known as occupational sources of cadmium exposure. Non-occupational sources of cadmium exposure may include smoking, diet, and house dust [9].

Role of Cadmium on Carbohydrates Metabolism

Effect of Cadmium Glycolysis

Glycolysis is a process of conversion of a six-carbon compound into three-carbon compounds. This process occurs in the cytoplasm [10]. Glucose is converted into glucose-6-phosphate (G-6-P) by the mechanism of phosphorylation with the help of an enzyme glucokinase [11]. The G-6-P is converted into fructose-6-phosphate (F-6-P) by an enzyme phosphohexose isomerase. F-6-P is phosphorylated by an enzyme phosphofructokinase to form fructose 1, 6-bisphosphate. Fructose 1,

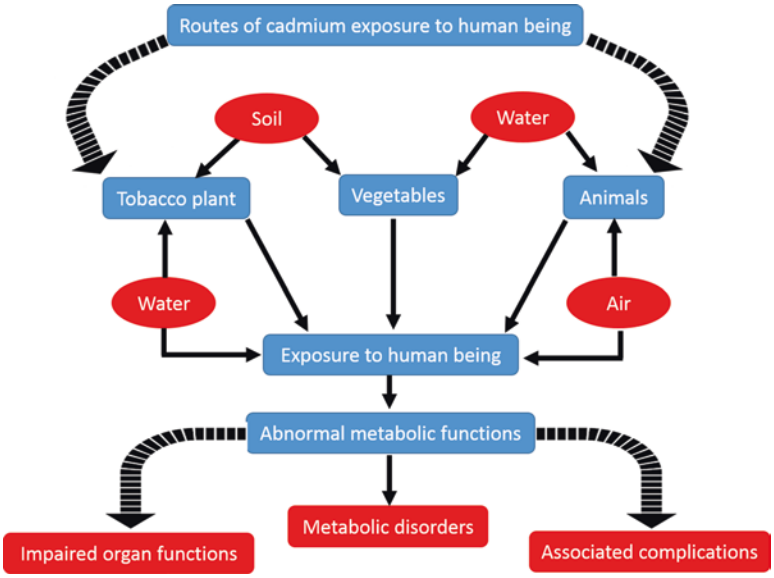

Fig. 13.1 Schematic representation of routes for cadmium exposure to human beings. Cadmium present in the soil, water, and air. It enters into the human being via vegetables, tobacco plant, and animals

6-bisphosphate is broken down to glyceraldehyde-3-phosphate (G-3-P) and dihydroxyacetone phosphate (DHAP), which is catalyzed by an enzyme aldolase. Then fructose 1,6-bisphosphate passes by several series of chemical reactions and conversion of phosphoenolpyruvate into pyruvate by utilizing an enzyme pyruvate kinase [10].

It has been demonstrated [12] that the glycolysis process can be limited by cadmium exposure because it has great potential to decrease the level of phosphofructokinase that is involved in the glycolysis process as shown in Fig. 13.1. The studies also show that cadmium exposure alters the chemical composition of muscles and liver [13]. Cadmium is also responsible to increase the activity of some enzymes that are responsible for many catabolic processes such as glutamate dehydrogenase, amino acid oxidase, and xanthine oxidase [14]. Several studies show that cadmium has an adverse effect on metabolic enzymes [15] and antioxidants [16, 17] and also on metallothionein expression [18, 19].

Cadmium has great potential to inhibit the hexokinase and phosphofructokinase by a mechanism in which cadmium has a great affinity towards a pair of free electrons present in the cysteine—SH group. Hexokinase and phosphofructokinase structure show that it has a great number of cysteine residues [20]. Studies revealed that by increasing the cadmium concentration, glycolysis can be inhibited as discussed earlier. The same case is observed for pyruvate kinase enzymes that are involved in glycolysis [21].

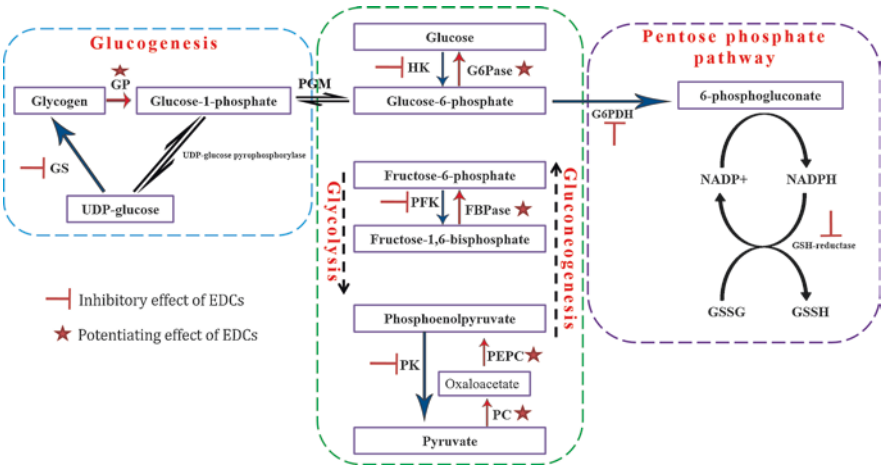

Fig. 13.2 Schematic representation of the mechanism of cadmium and arsenic interfering with enzymes that are involved in carbohydrates metabolism. Adopted from [12]. *GP* glycogen phosphorylase, *GS* glycogen synthetase, *UDP* uridine diphosphate glucose, *PGM* phosphoglucomutase, *HK* hexokinase, *G6Pase* glucose-6-phosphatase, *PFK* phosphofructokinase, *FBase* fructose-1,6-bisphosphatase, *PK* pyruvate kinase, *PC* pyruvate carboxylase, *PEPC* phosphoenolpyruvate carboxykinase, *G6PDH* glucose-6-phosphate dehydrogenase, *NADP* nicotinamide adenine dinucleotide phosphate, *GSH* glutathione

Effect of Cadmium Pentose Phosphate Pathway

Pentose phosphate pathway consists of two steps, the first step is the oxidative production of NADPH and the second step is non-oxidative inter-conversion of sugar [22]. Pentose phosphate pathway is a biochemical process that is parallel to glycolysis and it is a vital source for the production of NADPH [23]. In the process of glycolysis, glucose-6-phosphate is produced on which glucose-6-phosphate dehydrogenase converts it into 6-phosphogluconate. In this process, NADPH is produced which is used to maintain the level of glutathione in a reduced form whose function to kill the oxidative metabolites that are dangerous [24]. Cadmium has great potential to decrease the level of glutathione by inhibiting the activity of glucose-6-phosphate dehydrogenase (Fig. 13.2). The decreased activity of glucose-6-phosphate dehydrogenase may cause the induction of diabetes mellitus due to the oxidative stress-induced by oxidation [25]. The studies also show that the production of glucose-6-phosphate is decreased due to inhibition of hexokinase, an enzyme involved in glycolysis, and pentose phosphate pathway suppressed due to reduced level of glucose-6-phosphate [26].

Effect of Cadmium Glycogenolysis

In the process of glycogenolysis, glycogen is phosphorylated by glycogen phosphorylase and as a result, glucose-1-phosphate is produced. Glucose-1-phosphate is converted into glucose-6-phosphate and this reaction is catalyzed by an enzyme

phosphoglucomutase [27]. The experimental study reveals that the storage ability of glycogen in animals is decreased due to the exposure of heavy metals such as cadmium [28]. The phenomenon of glycogenolysis occurs due to a higher level of glycogen phosphorylase and its activity. The glycogen level may be reduced due to decreased activity of glycogen transferase. The decrease in the production of glucose-6-phosphate which is a very essential substance for glycogen synthesis may occur due to reducing the glucokinase activity [29].

If cadmium is exposed to placenta, then increased glycogen phosphorylase activity is observed [30]. Exposure of cadmium may increase the level of cortisol in plasma which may contribute to the activation of glycogenolysis [31]. Cadmium has the ability to accumulate in the pancreas and increases oxidative stress [32]. Cadmium is divalent which has the ability to interact with thiol group and zinc-binding site, which is generally present in proteins [33]. It has been revealed that chronic exposure of cadmium has a positive effect on the activity of serum amylase [34].

Effect of Cadmium Gluconeogenesis

In gluconeogenesis, pyruvate is formed from amino acids and lactate then transported into mitochondria from the cytosol. In mitochondria, pyruvate is converted into oxaloacetate with the help of an enzyme pyruvate carboxylase. Phosphoenolpyruvate carboxykinase acts on oxaloacetate and converts it into phosphoenolpyruvate. Then phosphoenolpyruvate is passed through a series of reactions and converted into fructose-6-phosphate. Then it is converted into glucose-6-phosphate by an enzyme phosphohexose isomerase that acts on fructose-6-phosphate. Finally, glucose-6-phosphate is converted into glucose after releasing the phosphate group [35].

Only a high dose of cadmium has an effect on enzymes that are involved in gluconeogenesis such as glucose-6-phosphatase, phosphoenolpyruvate carboxykinase, and fructose 1, 6-bisphosphatase [36]. It has been proposed that phosphoenolpyruvate carboxykinase is very important to target to treat diabetes mellitus associated with hyperglycemia [12].

Effect of Cadmium on Lipid Metabolism

The exposure of cadmium has a great potential on acetyl CoA carboxylase and fatty acid synthase that is involved in the synthesis of fatty acids [37]. Cadmium induces the lipid peroxidation of polyunsaturated fatty acids [38]. Chronic exposure to cadmium causes impairment in the storage and metabolism of lipids. Higher mobilization of lipids to mitochondria cause lower lipid content and decrease the level of triglycerides and ATP [39]. Further exposure to cadmium decreases the

level of NADPH. Cadmium has a negative impact on digestion, transportation, synthesis of fatty acids, and even on the metabolism of fatty acids [38].

Arsenic

Sources and Exposure

Arsenic is naturally present in the earth's crust and it is a very toxic element in an inorganic form that is present in air, land, and water. Exposure of arsenic to human beings (Fig. 13.3) is mostly through drinking contaminated water, using this contaminated water in the preparation of food and processing in the industries [40]. Arsenic contents are also found in the smoke of a cigarette. It is proved that by smoking a single cigarette, about 0.25 μg inhalation of arsenic occurs. Arsenic can be exposed to humans by the skin when there is the frequent use of cosmetic products [41].

Effect Arsenic on Carbohydrates Metabolism

Arsenic has the potential to inhibit the activity of hexokinase [42] production of ATP by substituting the phosphate group of ATP with arsenate, this process is known as arsenolysis [43]. The ability of arsenic to replace the phosphate group is due to its structural similarity with the phosphate group [44]. This process may occur during oxidative phosphorylation and as a result, adenosine diphosphate arsenate is produced (Fig. 13.4). Arsenic can react with glucose to form glucose-6-arsenate. Similarly, when arsenic reacts with gluconate it can produce 6-arsenogluconate [45]. Trivalent arsenicals can inhibit many enzymes that participate in the metabolism of carbohydrates such as α-ketoglutarate dehydrogenase, pyruvate dehydrogenase, and succinyl COA synthase. One of these following enzymes, pyruvate dehydrogenase is highly sensitive to arsenic toxicity. This causes a reduction in the production of ATP [12].

Arsenic-Induced Diabetes Mellitus

The subjects that are exposed to arsenic show similar symptoms as a patient suffering from type 2 diabetes mellitus [46].This is due to the same pathophysiology of T2DM which is induced by arsenic toxicity (Fig. 13.4). The possible pathway through which arsenic can induce diabetes mellitus has been well determined [47].

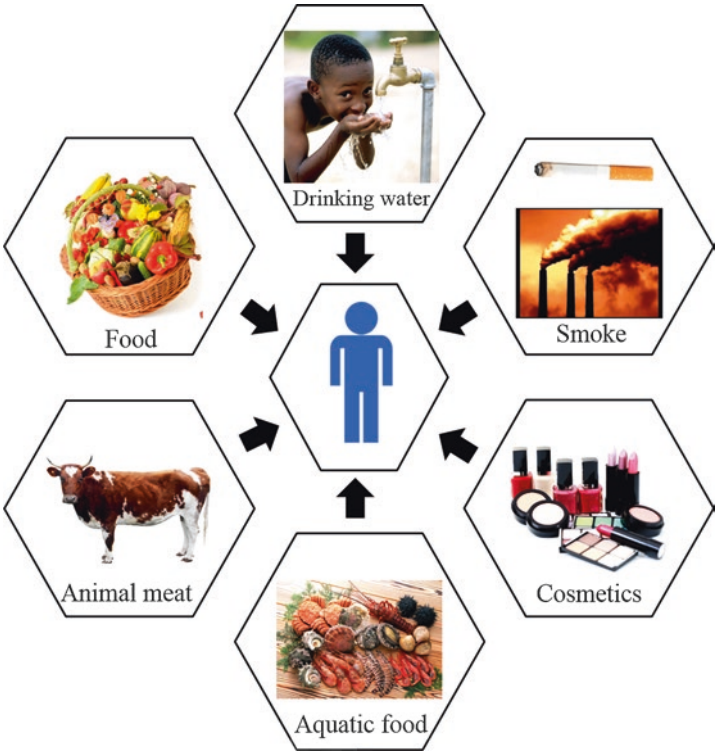

Fig. 13.3 Routes of arsenic exposure to human beings

Arsenic can induce oxidative stress by suppressing the antioxidant enzyme [48]. Arsenic can induce adverse effects on health by increasing the production of reactive oxygen species [49]. The chief house for the production of reactive oxygen species is mitochondria which may be due to the alteration in electron transfer through respiratory chain that enhances the production of hydrogen peroxide, hydroxyl radicals and superoxide anion [50].

Sulfhydryl group present in glucose transporter at the outer surface of the plasma membrane can form a bond with a polypeptide chain of insulin [51]. This sulfhydryl group has an essential role in the transportation of glucose either insulin-dependent or insulin-independent [52]. Arsenic has a high affinity for enzyme-containing thiols group and inhibits the binding of a substrate with the active site of an enzyme (Fig. 13.4). Trivalent arsenate reacts with molecules containing sulfhydryl group such as glutathione and cysteine [53]. Arsenic can induce alteration in the expression of genes that causes diabetes. Due to arsenic, the expression of mRNA and secretion of insulin is decreased [54]. The most important gene for a transcription factor peroxisome proliferative-activated receptor-γ control expression of a gene for the sensitivity of insulin. Arsenic has the ability to alter the expression of this gene and as a result synthesis of mRNA is inhibited and adipocytes differentiation is reversed [55].

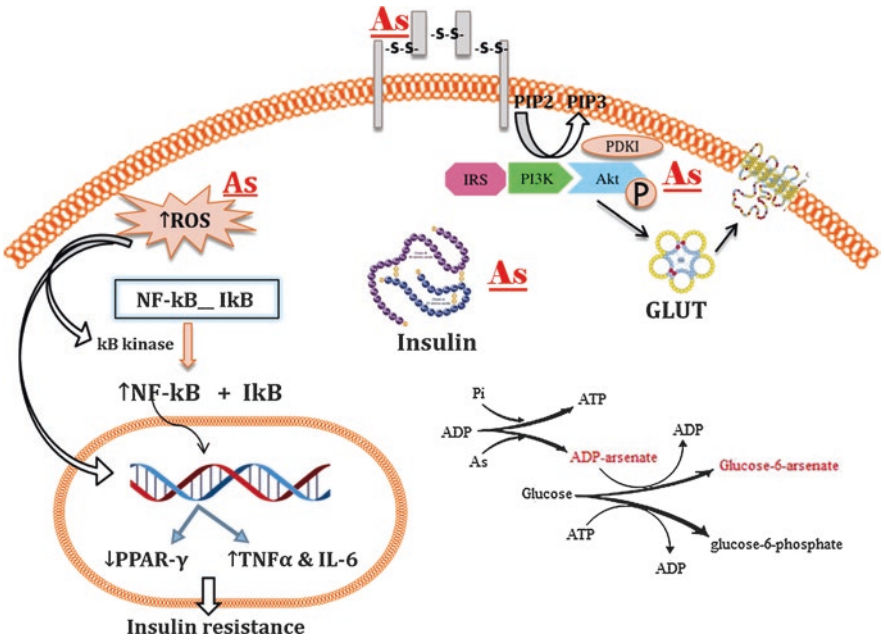

Fig. 13.4 Role of arsenic as an endocrine disruptor. Arsenic binds with a disulfide bridge present in insulin and insulin receptors and makes them non-functional. Arsenic impairs the translocation of GLUT by decreasing the phosphorylation of Akt. Arsenic competes with Pi and binds with ADP in order to make ADP-arsenate that is subsequently used in the formation of glucose-6-arsenate. Arsenic causes the elevation of oxidative stress level through which it increases the expression of pro-inflammatory cytokines (TNF-α and IL-6) and decreases the expression of PPAR-γ and these two factors play a key role in the development of insulin resistance. Adopted from [12]. *As* arsenic, *ROS* reactive oxygen species, *NF-kB* nuclear factor kappa B, *PPAR-γ* Peroxisome proliferator-activated receptor-gamma, *TNF-α* tumor necrosis factor-alpha, *IL-6* interleukin-6, *PIP2* Phosphatidylinositol 4,5-bisphosphate, *PIP3* phosphatidylinositol (3,4,5)-trisphosphate, *IRS* insulin receptor substrate, *PI3k* phosphoinositide 3-kinase, *GLUT* glucose transporter, *Pi* inorganic phosphorus, *ADP* adenosine diphosphate, *ATP* adenosine triphosphate

Lead

Sources and Exposure

Lead is a toxic metal, which is widely used and responsible for contamination in the environment and many health-related problems. The common sources of lead are found in the environment and mainly in food and smoking, drinking water, industrial process, and domestic sources [56]. The common route of exposure to lead is inhalation and ingestion. Inhalation of lead particles may be due to the burning of lead-containing materials. The lead may produce during the process of smelting, deterioration of lead-coated paint and by using gasoline loaded with lead. The ingestion of lead may take place due to lead-contaminated soil, water, and food

[47]. Another important pathway of lead intake is gastrointestinal absorption and retention but it depends upon the chemical environment of gastrointestinal lumen and iron stored in GIT [57].

Lead-Induced Oxidative Stress

Lead induces oxidative stress by interfering with many biochemical processes (Fig. 13.5). Lead has the ability to mimic or inhibit the calcium action by interacting with proteins. The biological molecules that are bound with lead, have not the ability to perform a number of biochemical processes. Lead has the ability to bind with sulfhydryl group and amide group present in enzymes, as a result, alter the configuration of enzymes and diminish the activity of enzymes. Lead also interferes with the transport of some cations by exhibiting the competition with other metallic cations for binding with the active site of enzymes [5]. This oxidative damage of membrane induced by lead is due to a change in fatty acids composition present in the membrane [59].

The lipid peroxidation induces oxidative stress and the production of reactive oxygen species in the lipid membrane. These free radicals abstract the electron from lipids that are present in the membrane and cause oxidative damage to the cell membrane. The free radicals are also responsible for the oxidation of hemoglobin and the destruction of red blood cells. The oxidation of lipids and hemoglobin results due to inhibition of δ-*aminolevulinate dehydratase*(ALAD), the substrate level of δ-aminolaevulinic acid (ALA) is increased in the blood and urine. The generation of superoxide and hydrogen peroxide results due to the elevated level of ALA. These oxides and peroxides react with oxyhemoglobins and hydroxyl radicals generated [60]. Lead has the ability to form a covalent bond with sulfhydryl group of antioxidant enzymes such as glutathione (GSH) and causes inactivation of this enzyme. The level of GSH is decreased which is not compensated by a γ-glutamyl cycle that is also responsible for the synthesis of GSH from cysteine [61]. Lead has the ability to bind with an enzyme ALAD, glutathione peroxidase (GP_X), glutathione reductase, and glutathione-S-transferase, causes inactivation of these enzymes, as a result, depresses the level of GSH [62]. Due to exposure of lead, alteration in gene expression occurs. The mechanism that is involved in alteration of gene expression is binding of lead with DNA associated protein, protamine, by interaction with zinc-binding site [63].

Lead has the ability to interact with enzymes that catalyze the synthesis of vitamin D and involve in the maintenance of the cell membrane. Lead disintegrates the cell membrane and RBCs with a membrane that has no integrity become fragile and results in anemia [64]. Lead also affects glucose-6-phosphate dehydrogenase, the enzyme responsible for catalyzing the initial step in the pentose phosphate pathway. Lead enhances the level of this enzyme in RBCs in human beings [58].

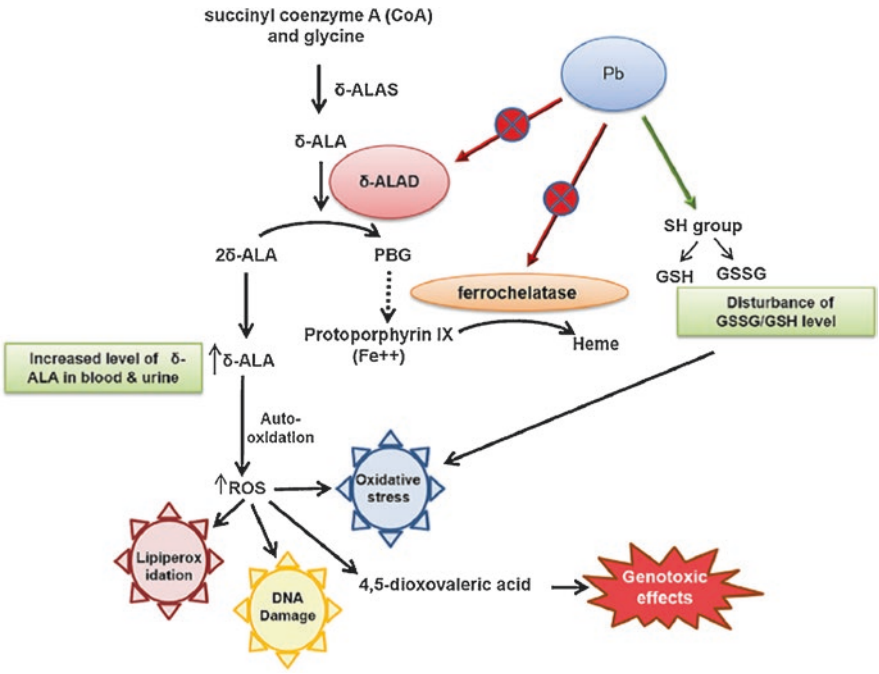

Fig. 13.5 Schematic representation of the mechanism of toxic effects of lead. Lead exposure causes anemia because of interference with heme-synthesis. δ-aminolevulinic acid dehydratase (δ-ALAD) enzyme is inhibited resulting in increased δ-aminolevulinic acid (δ-ALA) levels which can cause oxidative stress and may result in the production of genotoxic effects. Adopted from [58]

Lead-Induced Inflammatory Responses

Lead exhibits a negative impact on the immune system which is an important key element for the process of inflammation and plays a defensive role in injury within a living organism [65]. Lead exposure does not cause complete deficiencies of immune cells but it has a negative impact on the regulation of the immune system [66]. COX-2, an enzyme that is responsible for catalyzing the formation of prostaglandins H_2 from arachidonic acid. The resultant prostaglandins H_2 are involved in a unique series of enzymatic and non-enzymatic reactions for the formation of primary prostanoids; PGE2, PGF2α, PGI2, PGD2, and TXA2, and also the generation of reactive oxygen species [67]. Lead has the ability to influence the COX-2 gene by alteration in a *nuclear factor of activated T-cells*(NFAT) which is a transcription factor. Lead causes mutation in the NFAT binding site which is responsible for the eradication of COX-2 gene transcription [68]. IL-8 which has the ability to exhibit antioxidant response, is also bound with Nrf2. Lead is responsible for activation of IL-8 synthesis but their secretion depends upon Nrf2. The blocking of Nrf2, by small interfering RNA (siRNA), causes the complete blocking of transcription, translation, and secretion of IL-8 produced by lead [69].

Zinc

Zinc is a very important element and has an essential role in many events that occur in the cell. Zinc plays an important role in the functioning of enzymes when acting as a cofactor and also plays an important role in transcription [70]. Zinc is present as an integral constituent in a large number of enzymes and proteins and contributes to a wide range of metabolic processes such as carbohydrates metabolism, lipid metabolism, protein metabolism, and generation and degradation of nucleic acid [71]. Zinc has a unique role in metabolic syndrome by participating in cell events such as the expression of cytokines and suppression of inflammation. Zinc is responsible for activating antioxidant enzymes that reduce the level of reactive oxygen species which in return decreases stress-induced by oxidation. Zinc is also present in supplement whose function to improve blood pressure, level of glucose and cholesterol in the body. This suggests that zinc plays an important role in the regression of metabolic syndrome [72].

Effect of Zinc on Oxidative Stress

Oxidative stress is strongly associated with metabolic syndrome and has a connection with it through dyslipidemia, hypertension, diabetes, and obesity [73]. Zinc has the potential to inhibit the production of reactive oxygen species including hydrogen peroxide, superoxide anion, and hydroxyl radical [74]. Zinc also inhibits the reactive nitrogen species such as peroxynitrite [75]. Zinc also has an antioxidant effect by direct-acting on antioxidant proteins and the production of structurally modified metallothionein. Zinc performs the antioxidant activity by direct binding of zinc ion with thiol groups [76].

Effect of Zinc on Lipid Metabolism

In the living organisms, the lipid is accumulated in adipose tissues which lead towards obesity. Previous studies show that there is a connection between zinc serum level and metabolism of lipids. Zinc intake causes a decrease in the level of total cholesterol, triglycerides, and low-density lipoprotein cholesterol, and also causes an increase in the level of HDL cholesterol [72]. Leptin is a hormone produced by adipocytes which play an important role in the regulation of energy by increased energy expenditure and reduce the need for food uptake [77]. Zinc status is also an essential factor for determining the normal functioning of adipocytes and for the production of leptin for maintenance of negative feedback which is mediated by leptin. Zinc intake in obese patients who are resistant to leptin increases the serum leptin level and helps in the improvement of weight that is associated with metabolism [78].

Zinc has a significant role in adipokines. Zinc helps in the oligomerization of adiponectin which is a high molecular weight molecule by modulation of disulfide bond formation [79]. There is the existence of a positive relationship between adiponectin and serum leptin level in obese patients [80]. Adipokine, Zinc-α-2-glycoprotein is reduced in obesity, high fat diet, and inflammatory stimuli. Zinc-α-2-glycoprotein is responsible for the regulation of lipid metabolism in adipose tissues. Zinc-α-2-glycoprotein decreases the level of fatty acid synthase, acyl-coenzyme A and acetyl-coenzyme A carboxylase 1. It causes an increase in the hormone-sensitive lipase activity as a result of lipolysis occur and decreases in lipogenesis [72].

Conclusion

Heavy metals are substances which have high density and can cause toxicity to a human being even at very small concentration. The major source for exposure to heavy metal is an environment and anthropogenic sources. These metals expose to human beings may be by ingestion and inhalation. Heavy metals have a major contribution in inducing the various metabolic disorders that lead to cardiovascular diseases as endocrine-disrupting chemicals. Some heavy metals such as arsenic, cadmium, and lead show significant harm to health. Cadmium is a major contributor to disrupting carbohydrates and lipid metabolism and leads to various disease conditions. Arsenic is responsible for inducing diabetes mellitus type 2 by various different mechanisms such as alter gene expression, glucose transportation, and glucose metabolism. Lead has significant potential to induce oxidative stress and inflammatory response which causes various metabolic syndromes. Zinc is a necessary element that plays an important role in the prevention of metabolic syndrome by reducing reactive oxygen species and altering lipid metabolism.

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Conflict of Interest The authors declare that there is no conflict of interest.

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Chapter 14
Role of Flame-Retardants as EDCs in Metabolic Disorders

Talib Hussain, Abid Mehmood Yousaf, Muhammad Usman Ghori, Ikram Ullah Khan, Tahir Ali Chohan, Syed A. A. Rizvi, and Yasser Shahzad

Abstract The destructive potential of fire is well known and thus it makes sense to prevent it from happening at all, or slow its rate of spread and to be able to stop it as soon as it happens in undesirable situations. Flame retardants (FRs), as the name indicates, are chemical substances with the capability of slowing down or preventing the growth of fire, have been used in many households and industrial products for a while now. Many kinds of FRs are currently in use, such as halogenated, organophosphate, nitrogenous, inorganic, and intumescent coatings. These products are also well known to have many side effects, including carcinogenicity, reproductive toxicity, endocrine disruption, and immune system disorders. Not all fire retardants are made or function the same way thus vary in extent of fire-retardant capacity as well as toxic side effects. Herein we succinctly describe various classes of chemical FRs, and associated biological hazards to humans. We have also described

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underlying mechanisms or pathways that may possibly be involved in inducing endocrine disruption leading to obesity, diabetes, oxidative stress, and inflammatory responses.

Keywords Biological hazard · Brominated fire retardants · Obesity · Oxidative stress · Type 2 diabetes

Introduction

The objective of this chapter is to provide a succinct overview of a specific group of chemicals, namely flame retardants (FRs) that are known to have endocrinal disruptive properties. A number of industries producing various daily-life commodities utilize FRs for the protection of goods from being burnt out by the fire. In spite of enforcement of strict safety protocols, there is a possibility of such chemicals to escape into the environment as pollutants. Pollutants, by virtue of their nature, are chemicals that are exogenous to the environment; thus, pose a threat not only to humans but also to flora and fauna of the ecosystem [1]. Bioremediation in the ecosystem is responsible for degrading indigenous pollutants to clear up the environment; however, chemicals such as FRs are often resistant to biodegradation, hence are hazardous [2]. Some chemicals for industrial applications were designed with long half-lives for their cost-effectiveness, however ended up as environmental hazards owing to an extremely slow biodegradation [3]. Endocrinal system in humans and animals plays a vital role in ensuring the homeostasis. The endocrine system includes various organs consisting of endocrinal glands such as thyroid, parathyroid, adrenal, pituitary, and pineal. Endocrine system also consists of single cells and small clusters of neuroendocrine cells in various organs such as the lung and gastrointestinal tract, and the paraganglia [4]. On a pharmacological viewpoint, endocrine disruption caused by the chemicals can have serious health issues including obesity, diabetes and may lead to development of severe malignancies, such as breast, prostate, and testicular cancers [5]. Recent epidemiological data have shown a link between EDCs and metabolic diseases. While experimental data based on in vitro studies and those executed on various animal models have suggested multiple possible pathways by which EDCs alter normal hormonal functions and promote metabolic disease, the exact mechanisms remain elusive [6]. To this end, our focus in this chapter will be on various types of FRs that have majorly polluted our environment and the associated human health risks pertaining to endocrinal disorders as a result of exposure to this particular pollutant group.

Flammability and the Flame Retardants

Flammability is a process that involves various steps before a substance is completely destroyed by the fire. These steps include (a) preheating of the material, (b) decomposition, (c) ignition, and (d) combustion and propagation. When an external source heats the materials, it results in an increase in the temperature of the material at a rate dependent upon the intensity of the ignition source, thermal conductivity of the material, specific heat of the material, and latent heat of fusion and vaporization of the material. An extreme rise in a material's temperature can cause decomposition of the materials and the weak bonds of materials start to break down the material into gaseous compounds. An increasing concentration of the decomposed gaseous compounds allows for sustained oxidation in the presence of an ignition source and the available oxygen-rich environment makes the material ignite without the need of the ignition source, leading to the self-propagating combustion of the material [7]. However, decreasing the rate of heating, ignition, and combustion by the addition of specific chemicals that can physically or chemically hinder the flammability process can significantly retard the flammability and such chemicals are dubbed as FRs.

FRs have the ability to constrain, minimize, or delay the spread of fire by quashing the chemical reaction in the fire. They may also work by creating an external protective layer on a material [8], thereby serving as an insulation coating to reduce the chances of catching fire by decreasing the rate of heating. FRs have found their use in various daily-life products, for example plastics, textiles, electronics, construction materials, and furnishing foams to reduce fire hazards [9], thus the market share of FRs is worth billions of dollars. In 2016, an estimated worldwide consumption was 2.3 million metric tons with an annual increase in production by 3% globally [10].

Based on their method of incorporation in polymers, FRs are either additive or reactive [11]. Additive FRs are usually mixed or dissolved within the polymeric materials, while reactive type retardants are chemically attached with the polymeric materials through covalent bonds [1, 11]. Most of the additive FRs are volatile and may leach out in the environment easily, whereas reactive mixtures tend to leach out far less than the additive counterpart does. Due to their increasing use, widespread exposure within the environment with FRs is inevitable and many documented evidences show the presence of FRs in various environmental media, including indoor and outdoor air [12], water (surface or groundwater) [13], oceans [14] and even in human milk [15]. Thus, FRs present serious health risks to humans and wildlife [16].

Based on their activity, FRs work either in their vapor phase or the condensed phase, as depicted in Fig. 14.1. Furthermore, they differ from each other by their mechanism of action and FRs may act through chemical or physical mechanisms to impede the combustion process during preheating, decomposition, ignition, and flame propagation [17, 18]. Overall, more than 175 different types of FRs are known, which are generally classified under five major categories that include halogenated, organophosphate, nitrogenous, inorganic, and intumescent coatings [19]. Here, we have briefly discussed various FRs.

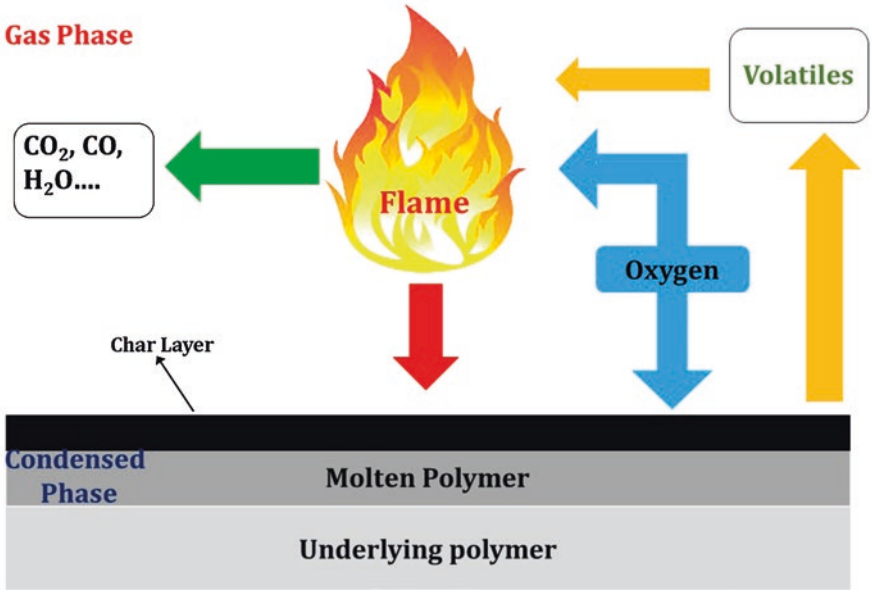

Fig. 14.1 A depiction of flame-retardant mechanisms illustrating different zones. Modified with permission from [106]

Halogenated FRs

Halogenated FRs interrupt combustion of materials mostly in their vapor phase. Most notable halogenated FRs are those which are based on chlorine or bromine; however, brominated chemicals remained the most used FRs. Chlorinated FRs include 1,4-di(2-hydroxyethoxy)-2,3,5,6-tetrachlorobenzene (TCHQD) and 1,4-di(ethoxycarbonylmethoxy)-2,3,5,6-tetrachlorobenzene (TCHQA). Among various brominated FRs (BFRs), the most notable are polybromodiphenyl ethers (PBDPE), polybrominated biphenyls (PBBP), decabromodiphenyl ethane (DBDPEh), tetrabromobisphenol A (TBBPA), brominated epoxy resin (BEP), and hexabromocyclododecane (HBCD) [18].

Organophosphate FRs

Due to restriction in the use of PBDPE as an FR, focus has been shifted toward the use of alternative FRs commercially [20]. Phosphorous is an abundant element, thus widely employed in various chemicals that have shown potential as FRs. For example phosphines, phosphine oxides, phosphonium compounds, phosphonates, phosphites, and phosphate are widely utilized as polymeric composites for fire retardancy [21].

Nitrogenous FRs

Some nitrogen containing compounds have also shown potential as halogen-free FRs owing to their relatively nontoxicity and high smoke suppression during combustion, and they are recyclable [22]. However, very few nitrogenous RFs have made it to the market. For example, melamine in polyurethane foams and melamine cyanurate in polyamides [23]. More recently, nitrogen-phosphorous synergies have also been utilized as materials for flame retardancy [24–27].

Inorganic FRs

Among various inorganic FRs, metal oxides and hydroxides are the most common. Magnesium hydroxide and aluminum hydroxide are widely used metal hydroxide FRs because of their low cost, reduced toxicity, anti-corrosive properties, and smoke suppression capability [28–30]. Other metal hydroxides that have been extensively utilized are layered double hydroxides (LDH) [31]. More recently, organic-inorganic nano-composites based on silicon materials, such as clay [32], kaolin [33], silsesquioxanes [34], and silicon dioxide (SiO_2) [35], have been widely accepted as a new concept for flame retardation.

Intumescent Coatings

Paints containing flame retardants are applied as thin coats thus have a limited amount of flame retardance which is insufficient to suppress fire or save the material from excessive heat. On the other hand, intumescent coatings applied as foams that swell and take a thick bubbly shape protect the material from fire or excessive heat [36]. Intumescent coatings are usually made of halogenated, organophosphate, nitrogenous, or inorganic FRs, individually or admixture of different FRs, and are applied as surface coatings. For example, an admixture of ammonium polyphosphate (nitrogen-phosphorous synergy) and diglycidyl ether of bisphenol A (DGEBA) epoxy resin, cured by low molecular weight polyamide is as an attractive intumescent coating with effective flame-retardant properties [37].

Flame Retardants as Environmental Pollutants

The extensive utilization of FRs in various commodities has given them access to the environment. FRs become pollutants by contamination of wastewaters or discharges from industry, such as producers of FRs for use and/or consumers of FRs

which incorporate them into other products, via leaking from products during preparation, upon breakdown of foam products or by discarding products, via percolation from landfills, incineration, and reprocessing of waste products or attachment onto the surface and interstices of dust particles [38]. Moreover, additive FRs are more prone to contaminate the environment than their reactive counterpart [39]. Once an FR makes its appearance in the environment, it can spread via transportation in water or deposition into sediment or become airborne by settling upon pollens and dust particles to reach far sites from the manufacture unit. Accordingly, FRs play a profound role in contamination of soil, water, air, and other ecosystems vastly [40–42]. The brominated flame retardants are employed extensively owing to their excellent performance, efficiency, and cost-effectiveness [43]. Hence, we will further focus on the impact of FRs, with special focus on BFRs such as polybromodiphenyl ethers (PBDPEs) and polybrominated biphenyls (PBBPs) on endocrine disruption and associated health issues pertaining to diabetes, obesity, oxidative stress, and inflammatory responses.

Endocrine Disruption by FRs

According to the U.S. Environmental Protection Agency (EPA), "*anendocrine disruptoris an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental process*" [5]. Several types of endocrine disruptors, also known as exogenous substances, ranging from natural to synthetic origin have been identified namely, tributyltin (TBT), diethylstilbestrol (DES), persistent organic pollutants (POPs), bisphenol A, polybrominated diphenyl ethers (PBDPEs), polybrominated biphenyls (PBBPs), parabens, and phytoestrogens [44]. Previous studies demonstrated that the exogenous substances discharged into the environment result in injurious effects on human and animal health. Such harmful implications in humans have been observed in the form of physiological disruption of the endocrine system, which basically regulates metabolism through hormonal control to provide desired level of energy and store it in the body as a fuel [44, 45]. Physiologically, EDCs act by various mechanisms that may alter the hormonal and homeostasis systems. This results in interference with nuclear/non-nuclear steroid hormone receptors, non-steroid neurotransmitter receptors (for example, serotonin receptor, dopamine receptor, and norepinephrine receptor), and orphan receptors. Enzymatic pathways related to steroid synthesis and metabolism may also be disturbed by EDC's exposure. Various other mechanisms that are important for endocrine and reproductive systems have also witnessed disturbances by EDCs [5].

Since our environment, indoors and outdoors, is heavily polluted by industrial/household waste and sewage, burning of litter in open places, automobile exhausts, and many other sources, the exposure of humans and animals to environmental pollutants is inevitable. Increasing understanding of endocrinology and perturbation in

normal hormonal functions by exposure to EDCs is an area of great interest and debate. A plethora of pollutants found in the environment may act similarly or differently, and consequently may disturb endocrine functions, thus it is very difficult to decouple the harmful effect of a certain pollutant from others. Consequently, many issues have arisen which are crucial to understanding the mechanism of actions and concerns of exposure to EDCs. For example, exposure to EDCs at an adult level may have different consequences compared with exposure at a fetal or infancy stage. Similarly, developmental complications may not be immediately apparent, instead may appear in adulthood or during aging. Individuals, or more generally a population are rarely exposed to a single EDC, rather a mixture of EDCs are present in the environment. In many instances, a synergy of chemicals may be involved, thus making it very difficult to pin point the exact pollutant producing negative effects on health. Dose–response is another factor that requires our attention. EDCs may evolve endocrine dysfunction at a low-dose level in certain individuals or population, and similar level of manifestations may require a high-dose level in other individuals or population. Lastly, transgenerational effects may arise, where the endocrine dysfunction appears in the subsequent generations [5]. Thus, all these factors play their role in understanding endocrine disruption by EDCs.

To this end, FRs are among the EDCs that are known to be hazardous to normal functioning hormones. Hence, we have presented a general picture of various metabolic mechanisms that are affected by the EDCs including most commonly used FRs. To remain in the scope of this chapter, a succinct overview of various metabolic pathways that are believed to be involved in the prognosis of obesity, diabetes, oxidative stress, and various inflammatory responses as a result of endocrine dysfunction by EDCs (particularly BFRs) is presented in the following section.

FRs Induced Obesity and Diabetes

Exposure to FRs may induce endocrinal disruption leading to specific abnormalities such as obesity, diabetes mellitus, or the improper functioning of thyroid hormones. Hence detailed studies are required to identify the classes of pollutant involved, sources, route of exposure, and mechanistic pathway of such inappropriate modulation of the endocrine system [46]. Several authors in recent years suggest that these exogenous substances potentially affect body hormonal control, causing imbalances in the regulatory system, resulting in severe complications such as an abnormal increase in body weight or abnormal functioning of the pancreas which leads to obesity and diabetes mellitus, respectively [44].

Obesity has become a critical health issue and WHO declared obesity as one of the major health issues in the world [47]. Obesity or excessive weight gain is associated with various metabolic disorders including insulin resistance, hyperinsulinemia, hypertension, and hyperlipidemia. All these problems collectively contribute toward the development of type-2 diabetes mellitus (T2D) and coronary heart disease. Genetics, poor diet, and insufficient exercise are considered as a

prime contributor of obesity. However, recent research has indicated another unheeded factor, i.e., environmental chemicals or EDCs which are a key source of air, water, and food contamination [48, 49]. Many EDCs have been identified to significantly alter the adipose tissue functioning in various animal models after developmental exposures, as depicted in Fig. 14.2. Although animal models have shown compelling evidence of obesogenicity yet endocrine disruption by EDCs in humans remains elusive [50].

We now know that BFRs have found a widespread use in daily life and a few of them have high production demands, such as PBDPEs, tetrabromobisphenol A (TBBPA), and hexabromocyclododecane (HBCD) [51]. Thus, their appearance in the environment is significant and inevitable. PBDPEs are the most commonly used flame retardant over the years. Being highly lipophilic dicyclic aromatic ethers, they are easily taken up by human adipose tissue where they can reside in high concentrations [52–54] and may appear in the breast milk [55, 56]. They are also found accumulated in mammals [57], fish [58], and birds [48, 59]. PBDPEs are formulated as a mixture of penta-, octa-, and decabromodiphenyl ethers, based on an average bromine content [8, 60, 61]. Depending on the position of attachment and number of bromine atoms, there are 209 PBDPE compounds, each termed congeners with a specific number [62]. PBDPEs are chemically and toxicologically analogous to polychlorinated biphenyls (PCBs), which are linked to hyperglycemia and dyslipid-

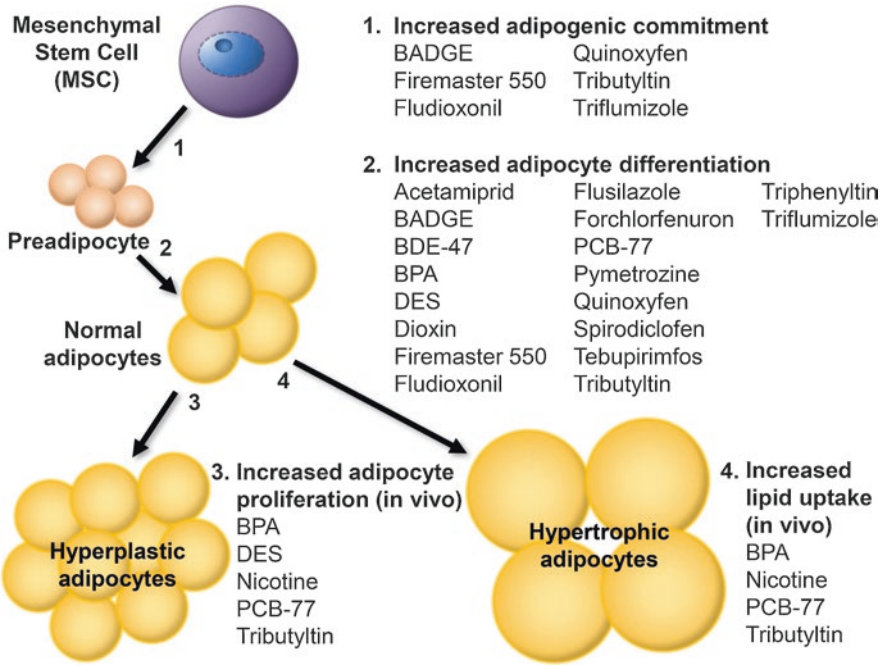

Fig. 14.2 Adipocyte formation pathways and various sites of action of EDCs. Reproduced with permission from [107]

emia [62]. The alteration in hormonal sensitivity of adipose tissue by PBDPEs has been examined in male rat [63]. The findings of this study showed marked increase in lipolysis and decrease in glucose oxidation, both of which are associated with obesity, insulin resistance, and type 2 diabetes [48, 64–66]. Thus, the abnormal health issues such as disturbance of lipid and glucose metabolism may be associated with PBDPEs [67].

The diabetogenesis may be correlated to environmental pollutants. Lee and coworkers [64, 68] draw attention regarding an influential factor, i.e., existence of obesity and diabetes in relation to environmental pollutants depending upon their high concentrations in blood. Figure 14.3 provides a mechanistic insight into various possible pathways where EDCs may act to deregulate the normal functioning of pancreas. In toxicology, theory of disruption of glucose and lipid metabolism in mammals by pollutants has been well established [69], yet EDC's effects on human require thorough toxicological and epidemiological studies. Most of the studies using animal models are acute exposures (i.e., less than 2 weeks) while few are chronic ones (i.e., more than 3 months) [70]. Although these results suggest that diabetes could be exacerbated on xenobiotics exposures but still biologically plausible explanation needs to prove this correlation. In recent past, Hugo and coworkers demonstrated that BPA (a common compound used in various plastic manufacturing and as a mixture in FR epoxy resin mixtures) at environmentally relevant doses (0.1 and 1 nM) inhibited the release of an adipocyte-specific hormone, namely adiponectin, which is believed to increase insulin sensitivity in

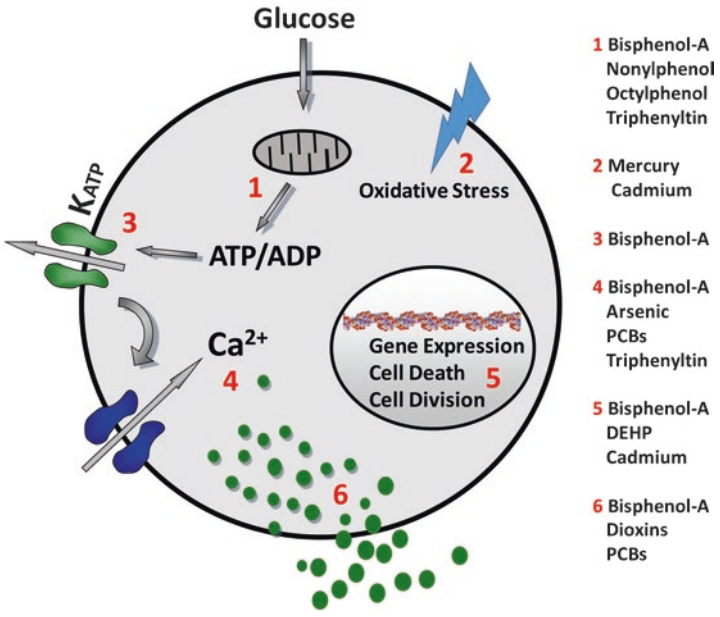

Fig. 14.3 Blood glucose level regulation by pancreatic beta cells and exposed site to metabolism disruptors. Reproduced with permission from [107]

humans. Consequently, an increased susceptibility to insulin resistance and obesogenicity may appear; however, the exact mechanism by which BPA acts remained poorly understood [71].

Hence detailed further investigations are required to provide substantial evidences which relate association of such health implications on exposure to environmental pollutants such as FRs [58, 72].

FRs Induced Oxidative Stress and Inflammatory Responses

In particular, polybrominated diphenyl ether and polybrominated biphenyls play a role in endocrine dysfunction, thus result in oxidative stress and inflammatory events [73, 74]. BFRs are produced and used extensively; accordingly, they are very prone to contaminate the environment, and affect human and animal health and homeostasis [75]. The human population is exposed primarily through food products, mostly from contaminated animal fats [76]. They are efficiently absorbed, distributed in the body, and deposited in adipose cells. They are bio-transformed or metabolized in the human body by the cytochrome P450 enzyme system, in particular, by cytochrome P450-dependent monooxygenase [76]. They can readily cross the placental barrier and are teratogenic; thus, they might have serious effects on a fetus [16]. They also appear in the breast milk of exposed humans; therefore, they can further affect a breast-feeding child [77, 78]. BFRs are a group of structurally similar chemical substances, consisting of two bromine-decorated aromatic rings. This structural similarity influences the toxic capability, and numerous congener's attachment to dioxin-receptor (aryl hydrocarbon receptor—AhR). In essence, most of the highly toxic congeners play insignificant part, as they are in very minute titer. However, some exceptions might be there which avidly bind with dioxin-receptor and result in dioxin-receptor mediated carcinogenic property. Some other similar consequences pertaining to structural similarity might include neuro-behavioral effects, the imbalance in thyroid hormone homeostasis, and the effects on the hepatic metabolic pathways [77].

Arene oxides and quinones, also known as highly reactive metabolic species, are produced owing to biotransformation of BFRs, are genotoxic and mutagenic. The production of reactive oxygen species (ROS), lipid peroxidation, oxidative and alkylating gene adducts can ultimately cause genotoxicity; thereby leading to the formation of oncogene which eventually initiates cancer. Thus, BFRs activate AhR which is a key to open the events associated with carcinogenesis mediated by dioxin-receptor. Due to persistent stimulation of the receptors, normal cell-cycle control and cell proliferation are lost, apoptosis is inhibited, cell-to-cell adhesion and signaling are impaired, and cell plasticity and invasiveness are increased [76]. From this angle, BFRs may induce tumors in rodents and cholangiocarcinomas in mice and rats [79].

TBBPA is a relatively new FR that made its entry in the market recently. Owing to its high efficiency, lipophilicity, and superior stability, it has been utilized as an

FR in many products [80], thus there is a great possibility TBBPA may contaminate the environment. TBBPA induces oxidative stress, as reported recently, which may lead to apoptosis in zebrafish embryos and larvae [81], while some other studies reported hepatotoxicity by the creation of reactive oxygen species (ROS) [82]. A recent study by Guan and co-workers revealed that TBBPA induces higher levels of ROS that leads to an increased oxidative stress level, which produces detrimental effects on mitochondria thereby promoting apoptosis, as depicted in Fig. 14.4 [83].

Furthermore, these compounds are also immune-toxicants and can compromise the normal functioning of the immune system. They can excite the production of inflammatory mediators. Vasiliu and co-workers in their study proved that no association exists between a brominated flame retardants serum titer and incidence of diabetes mellitus [84]. Although an earlier study found they may result in hypothyroidism and its associated disorders in individuals having prolonged exposure to their use [85]. A number of investigations have shown that BFRs exposure have reduced the serum levels of thyroxine (T4) hormone in rodents [86–89]. This is achieved by interfering with function and regulation of the thyroid gland, metabolism of thyroid hormone, and/or transportation mechanism of thyroid hormone [90]. BFRs are often linked with neoplasms in the thyroid gland in rodents [91]. Several animal studies have revealed that hypothyroidism due to BFRs is the consequence

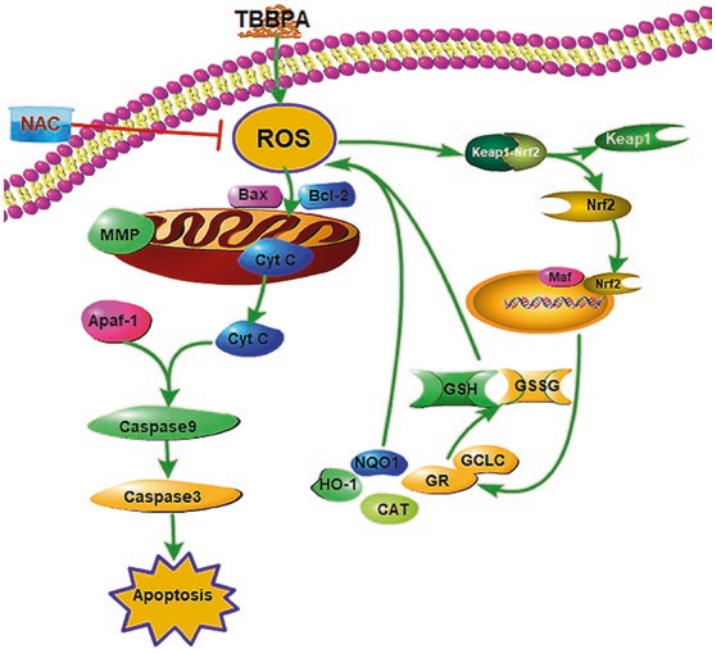

Fig. 14.4 TBBPA induces oxidative stress and mitochondrial damage leading to intracellular apoptosis. Reproduced with permission [83]

of interference with either thyroid hormone metabolism [92–94] or thyroid hormone transport [95–97].

Some BFRs can act as hormones, estrogen agonists, or antagonists, and can lead to serious consequences such as reproductive disorders and carcinogenesis. To investigate antagonistic activity of BFRs to estrogen, an in vitro receptor-mediated reporter gene assay employing human breast cancer cells was exploited. In this assay, an estrogen receptor-mediated luciferase reporter genome complex, which was decorated with three estrogen response characters, was presented and incorporated in the genetic material of the T47Dcells [98]. Introduction of xenobiotic estrogens leads to diffusion of chemical entities across the plasma membrane, attachment to the endogenous estrogen receptors, stimulation of the receptor, and ultimately, annexing to the ligand-receptor structure to estrogen response elements located in the promoter site of the luciferase gene. Thus, luciferase protein is tempted and conveniently measured by rupturing or lysing the cells, adding luciferin substrate, and quantifying light photon generation. In research studies with BFR exposure, brominated diphenyl ether-47 exhibited weak estrogenic activity compared with that of estradiol. Some polybrominated bisphenol resembling structures, such as monobromobisphenol A and dibromobisphenol A, demonstrated greater estrogenic activity than those of brominated diphenyl ethers. In other investigations, polybrominated biphenol tetrabromobisphenol A also demonstrated attachment to estrogen receptors, and encouraged proliferation of estrogen-dependent MCF-7 cells [99, 100] and MtT/E2 cells [101]. PBDPEs also exhibit antagonistic activity to estrogen when investigated in vitro at micromolar titers in conjunction with estradiol, including brominated diphenyl ether-153, brominated diphenyl ether-166, and brominated diphenyl ether-190 [97]. However, Villeneuve and co-workers could not find any compelling evidence of estrogenic potency of brominated diphenyl ether-47, brominated diphenyl ether-100, and brominated diphenyl ether-75 [102]. This incongruity might be attributed to estrogens that originate in human breast cancer cells (ER-CALUX) compared with the MVLN reporter gene assay [98]. Only a few research investigations on exclusive estrogenic properties of brominated flame retardants in vivo are available. Irrespective of its in vitro estrogenic effects, investigations involving *in ovo* introduction of tetrabromobisphenol A have demonstrated no estrogenic activity in birds, such as quail and chicken embryos [103]. This apparent deficiency in estrogenic characteristics might be owing to the prompt biotransformation of tetrabromobisphenol A in vivo, as revealed in both rats [104] and quail [105].

Conclusions

Fire has played a major role in shaping human society and is an essential component of many religions and ancient mythologies. Stopping or retarding unwanted fire has always been desired; this coupled with advances of chemical know-how, we have a variety of chemical substances for this specific task, known as fire retardants. With

over 175 distinctive types, they are mostly classified as halogenated, organophosphate, nitrogenous, inorganic, and intumescent coatings. Of them, the brominated flame retardants have had the most success and are also cost-effective and efficient. Due to the widespread use of FRs, they have polluted our ecosystem and many of these compounds have shown significant biological activity such as disruption of the endocrine system, causing obesity and diabetes, elucidating oxidative stress and inflammatory responses. With heightened awareness of the toxicities associated with the use of FRs and given their importance, the need for more efficient, safe, and cost-effective flame retardants is deepened and forthcoming new classes of improved fire retardants in the near future are imminent.

Conflict of Interest The authors declare that they do not have any conflict of interest for this article.

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Chapter 15
Role of Phthalates as EDCs in Metabolic Disorders

Tahir Farooq, Arruje Hameed, and Ali Raza

Abstract Phthalates are water-insoluble organic plasticizers which provide flexibility to PVC-plastics and make them useable in pharmaceutical industry, medical devices, clothing, and food packings. These plasticizers leach out from such articles as they are not chemically bound to polymeric materials and act as toxicants. These contaminants are found everywhere in the environment. Humans are always exposed to different kinds of phthalates through food, inhalation, personal care products, clothing, medication, nutritional supplements, etc. The hand to mouth behavior of infants increases the risk of phthalates exposure at the crucial phase of their growth and development. The phthalates or their metabolites act as agonist or antagonist ligands and disrupt the chemical signaling of the endocrine hormones thus are regarded as endocrine disrupting chemicals (EDCs). So the disrupted messaging by the hormones implicate a number of abnormalities, behavioral issues, and diseases like impaired neurodevelopment, decreased IQ and attention deficit, early puberty and fertility issues, sex anomalies, altered reproductive development, etc. The impaired endocrinal signaling cause perturbation of lipid and glucose homeostasis and result in obesity, overweight and insulin resistance and type II diabetes.

Keywords Phthalates · Toxicants · EDCs · Plasticizers · Hormone-signaling

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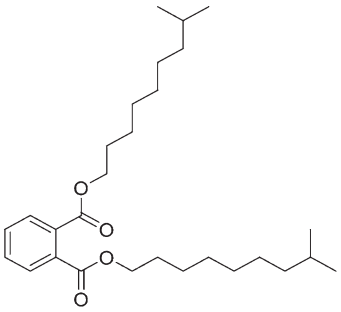
Introduction

Modern life heavily depends on synthetic plastics; however, a little is known about their complete toxicity and negative impacts on human health. Plastic is a blend of polymeric material like polyvinyl chloride (PVC) and a plasticizer, usually a synthetic chemical like phthalate (phthalic acid (PA) diesters) which imparts plasticity/flexibility in products proportionate to its quantity. Phthalates are high volume chemicals with wide spread applications in countless personal care products owing to their valuable characteristics and economical availability. From the last few decades, they are increasingly used in personal care products (perfumery and cosmetic industry), food packing, and medications. Being plasticizer in nature, they do not form any chemical bond with polymer matrices and the physical bonding is always highly susceptible to slight change in surrounding environment [1, 2]. A little change in environment in respect of temperature, pressure, pH, and exposure to irradiation (microwave heating and sunlight) accelerates their leaching into the surrounding environment. These leaches from plastic and other goods to water, soil, breathing air, food, drinks and to blood from medical devices pose serious hazardous threats to entire biota especially to human beings. Resultantly, ingestion has become the main route of exposure in humans which cause various dysfunctions. Most significantly, they pose serious threats to fetal development, and cause reproductive anomalies, obesity, and insulin resistance both in males and females [3, 4].

The first phthalate i.e. diethylhexyl phthalate (DEPH) was introduced in 1920 as a plasticizer; however, currently a number of phthalates are commercially available with ever increasing applications in human life. This year, the global market for phthalic anhydride (main reactant for the production of phthalates) has been expected to reach ten billion USD and this suggests a sharp rise in demand of phthalates in last few years (6.9 billion USD in 2013). The demand for HM phthalates (like DEHP and diisononyl phthalates) had been anticipated to rise to 6.75 million ton which was about 5.35 million tons 5 years ago [5]. This alarming increase in their unregulated usage indicates that they will implicate some very serious health hazards in near future around the globe. Due to the heavy utility of phthalates in routine life, we ingest them and their metabolites passively from breathing air, foods, and drinks with ultimate risks of endocrine disruption (Fig. 15.1).

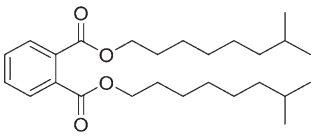
Mean and Route of Phthalates Entry

Over the years, phthalates have been recognized as deadly toxicants as they are omnipresent (in breathing air, clothing materials, food, and water) around us and all parts of human body have the capacity to absorb them. Humans are always exposed to different kinds of phthalates (Fig. 15.2) through food, inhalation, personal care products, clothing, medication, nutritional supplements etc. [6, 7].



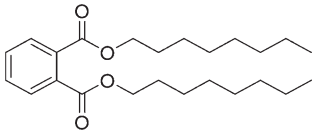
DIDP

Pharmaceutical, PVC flooring Cookware
plasticizer/softener in PVC



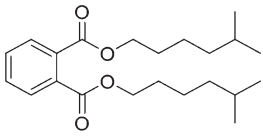
DINP

Resins, suractants, footwear, sealings,
lamination films, screen printing,
electric wire and cables



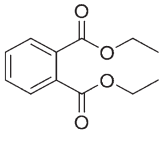
DOP

Shower curtains, wood coating, flooring,
medical and sanitary products, food packaging,
gloves, blood bags, dialysis equipmen, implants



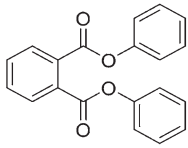
DnHP

mainly in automotives,
rubber and other plastic products



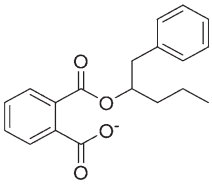
DEP

Mosquito repellents,
pharmaceutical packaging
persnonal care products
coatings



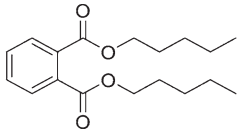
DPhP

plasticizer, polystyrene,
phenol, vinyl resins



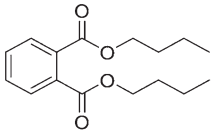
BBzP

personal care products, car-care
products, synthetic leather, packging,
adhesives, sealants, toys



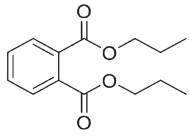
DnPP

paints/lacquers, fiberglass
and rubber grouting agents



DnBP

pharmaceutical, personal care products,
fragrance ingredients, varnishes, coating



DnPrP

adhesives, PVC resins

Fig. 15.1 Types of phthalates and their applications in daily life

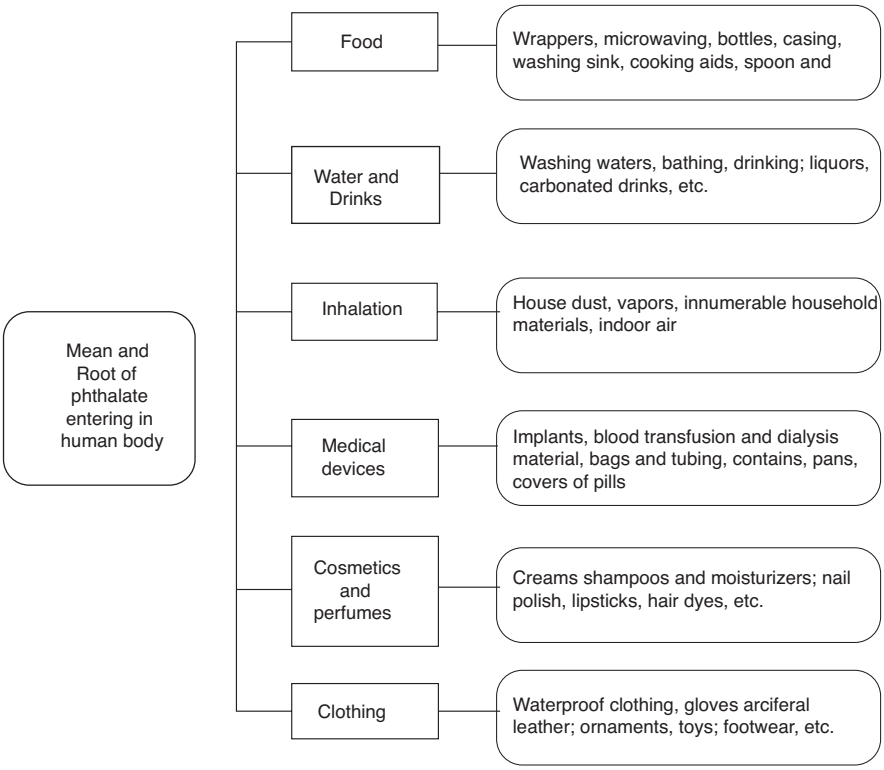


Fig. 15.2 Mean and route of phthalate entry

The hand to mouth behavior of infants increases the risk of phthalates exposure at the crucial phase of their growth and development. The fetuses and neonates are prone to severe toxicity of phthalates as they have the potential to cross placenta [8]. Different countries allow different permissible limits of phthalates in various products; the WHO allows DEHP 8 μg/L in drinking water while it should not exceed 6 μg/L in the USA. Urine is used as main biomonitoring source for the analyses of phthalates/metabolites as biomarker of type of phthalate exposure. However, various studies have also used other body fluids like serum, ovarian follicular fluid, semen, breast milk, amniotic fluid, and saliva for the assessment of various phthalates in human body. The body burden of phthalates is expressed in standard units as μg/Kg (body weight)/d (day) [9].

A recent study on fast food consumers (N = 8877) in the USA presented a vivid picture of the frightening higher levels of DINP (39%) and DEHP (23.8%), phthalate metabolites in urine samples [10]. According to another study, adults in the USA on average take nine phthalates in range of 0.673 for DEHP and 0.004 μg/Kg body weight/d for DMP [11]. In one such study in China, 14 phthalate metabolites were detected in urine samples with concentration ranging from 18.6 to 3160 ng/mL. The monophthalates of diethylhexyl, isobutyl, and butyl phthalates were detected as the

predominant phthalate metabolites while the daily intake of DEHP, DBP, and DEP was 5, 3.8, and 12.2 μg/Kgram body weight/day, respectively [12]. According to one such study in New Delhi, India, researchers analyzed dust, in- and outdoor air samples, food items, and drinking water using sophisticated technique like GC-MS and found DEHP as the major toxic compound approximately 70 μg/Kg body weight/d along with others like BBP, DMP, and DnBP with detectable limits. Further, they concluded edibles and drinking water are the major source (more than 75%) of these residual phthalates [13].

Such studies have raised the alarms about the so common exposures, existence, and detection of phthalates in humans in developing as well as in developed countries. Considering the gravity of situation, researchers have developed a number of biomonitoring parameters using biological fluids like blood serum, breast milk, and mainly urine for the detection of body burden of phthalates and their primary and secondary metabolites. Correspondingly, a number of risk assessment strategies have been evolved over the years to avoid toxicant-mediated illness [14, 15].

Transformation

In general, the high molecular phthalates first get converted into hydrolytic monoesters and subsequent enzyme-mediated oxidation of alkyl chain produces more hydrophilic metabolites readily excreted through feces, sweat, and urine. These monoesters are excreted as such or they do experience phase-II biotransformation and get converted into more water soluble and easily excretable glucuronide conjugates (Fig. 15.3). The oxidative metabolites of DEHP (Fig. 15.4) namely mono(2-ethyl-5-hydroxylhexyl) phthalates (MEHHP) and mono(2-ethyl-5-oxylhexyl) phthalates (MEOHP) mainly undergo glucuronidation before excretion in human (Scheme 2). Similarly, the monoester metabolite of DEHP, the mono(2-ethylhexyl) phthalates (MEHP) gets transformed into glucuronide conjugates before its final excretion. The low molecular weight phthalates undergo hydrolysis of one of the ester in phase-I biotransformation [16, 17]. So the hydrolytic monoesters, oxidative metabolites, and biotransformed glucuronide conjugates should precisely be detected for the determination of body burden of phthalates for accurate risk assessment especially in human beings.

Phthalates as Endocrine Disrupting Chemicals

The glands located in thyroid, testes, ovaries, pancreas, kidneys, gastrointestinal system, and brain in human control a number of physiological functions through hormone secretions directly in circulatory system. These hormones do act as chemical messengers (Fig. 15.5) in the nature of steroids (secosteroids, glucocorticoids,

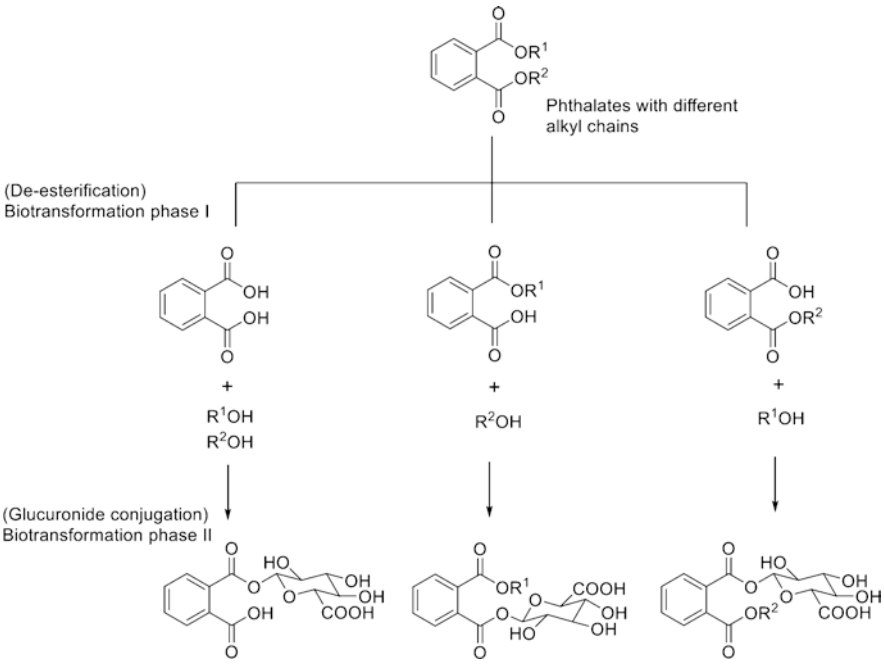


Fig. 15.3 Biotransformation of phthalates

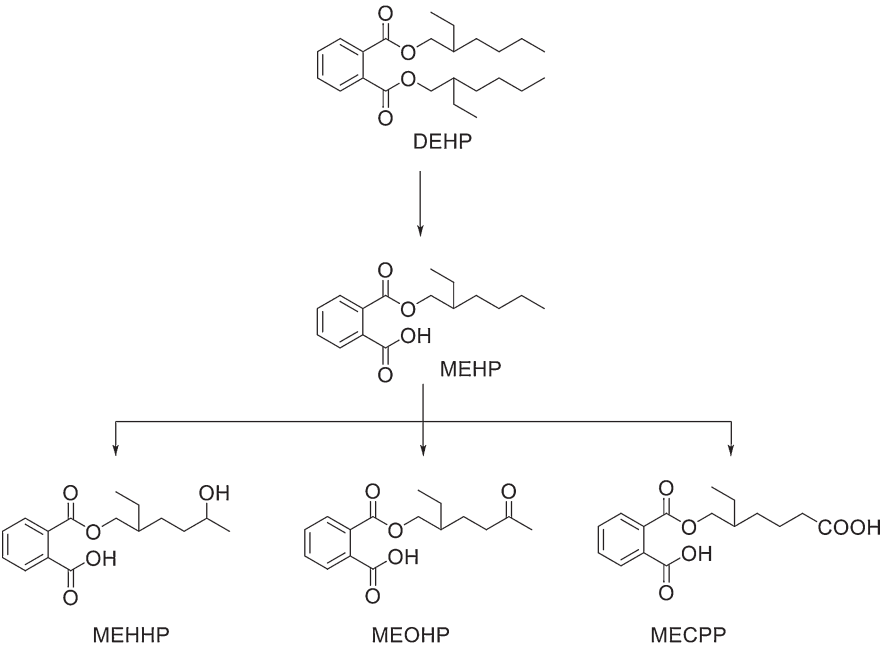


Fig. 15.4 DEHP and its metabolites

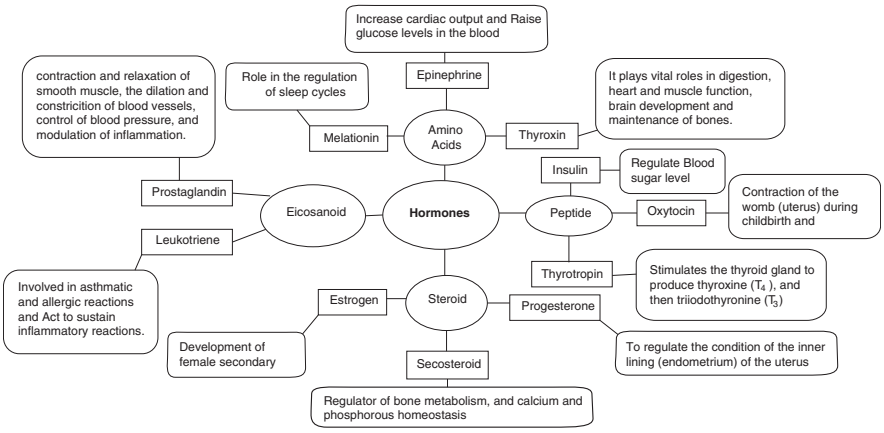


Fig. 15.5 Nature of hormones and their physiological functions

progesterone, estrogen, androgens, etc.), peptides (insulin, glucagon, thyrotropin, oxytocin, etc.), and amino acids (thyroxin, melatonin, epinephrine, etc.) [18].

Phthalates are lipophilic in nature thus gets absorbed readily in blood and subsequently biotransformed into hydrolytic, oxidative, and glucuronide conjugates (primary and secondary metabolites) with strong capacity to interact with the aforesaid hormones thus impair the normal physiological functions. The phthalates or their metabolites acts as agonist or antagonist ligands and disrupt the chemical signaling of the endocrine hormones, thus are regarded as endocrine disrupting chemicals (EDCs) [19]. Such unavoidable interactions of phthalates or their afore-mentioned metabolite do depend upon their biological half-life. The disruption of chemical signaling and the resultant dysfunctioning of physiological processes are proportionate to the half-life of interacting phthalates or their metabolites. So the disrupted messaging by the hormones implicate a number of behavioral issues, abnormalities, and diseases like impaired neurodevelopment, decreased IQ and attention deficit, fertility issues and early puberty in both genders, sex anomalies and altered reproductive development, obesity, issues of overweight, type II diabetes and insulin resistance, etc. [20, 21].

Obesity and Phthalates

The issues of overweight and obesity have significantly been correlated with phthalate exposure in a number of studies around the world. Phthalates are regarded as the major contributing factor for the obesity development through metabolic disruption. They show different associations in different sex and age groups thus level of obesity varies accordingly. In case of obese adults, the high molecular weight phthalates were found associated significantly with obesity. However, female adults found

to show their obesity association mainly with DEHP. While low molecular weight phthalates and their metabolites have shown association with obesity in adolescent and male children. The phthalates have established their direct linked on obesity-development independent of subject's physical activity and diet intake. The obesity in senior citizens was positively correlated with the prevalence of DEHP and its metabolites [22–24]. The lipid metabolism and its homeostasis is mainly regulated by hormone-assisted coordinated molecular signaling in normal physiological conditions. The phthalates interfere and disrupt the signaling mechanisms for the lipid metabolism through different channels and pathways [25, 26].

1. Thrifty phenotype-epigenetic modulation channel.
2. Phthalate-PPARγ-adipogenesis.
3. Phthalate-thyroid hormone channel.
4. Phthalates-PPARα-androgen channel.

Mainly hypothalamic-pituitary-gonad/thyroid along with PPAR channel the disrupted signaling for lipid metabolism and subsequent homeostasis. The PPAR mediate the nuclear signaling for lipogenesis in coordination and control of endocrine messaging. The phthalate binding to PPAR especially to PPARγ results in perturbed nuclear receptor signaling. The impaired glucose-homeostasis generally leads to lifestyle disease syndrome, obesity, and type II diabetes. The fatty acid metabolism processes often experience multiple disturbances in insulin-resistant individuals; as a result the fats get accumulated in skeletal muscles, endothelial cells, adipose tissues and liver; the insulin targets cells and tissues. Consequently, the situation leads to oxidative stress due to resultant acquired mitochondrial dysfunctions [27–30]. Generally, diet is considered as the main cause of obesity. However, phthalates and its metabolites alter the cell signaling mechanisms of nuclear receptors of obesity-related pathways well mechanized for lipid homeostasis.

Insulin Resistance, Type 2 Diabetes, and Phthalate Exposures

The higher level of blood sugars due to improper utility of insulin or due to inadequate insulin production has been considered as a major metabolic disorder. According to WHO report in 2016, the T2D is the main prevalence diabetes mellitus around the world [31]. In contrary to insulin-based considerations, many environmental factors do account for the onset and progression of chronic type 2 diabetes. In fact, numerous environmental toxicants like phthalates are supposed to act as activators of PPARs thus pose serious risks of diabetes. In fact, the development of β-beta cells get impaired due to the undesirable off-target interactions of PPARs (key regulators of glucose and lipid homeostasis) with phthalates [32]. In a number of studies, the urine and blood samples represented the presence of a number of phthalates/metabolites as markers in epidemiological studies. The impaired functioning of beta cells, decreased insulin sensitivity, and increased insulin resistance could be confirmed by the perceptible phthalate/metabolite levels along with fasting

and oral glucose tolerance test. The insulin resistance accounts more to induce diabetes than the beta cell dysfunctioning [33, 34].

A number of T2D related studies found the DEHP/metabolites as the main perceptible markers in their blood, serum, and urine samples. The dysfunctioning of β-cells, decreased insulin sensitivity, and increased insulin resistance were detected when obesogenic and diabetogenic characteristics were co-studied in one such study [35]. Over the years, concerns have raised due the high chances of phthalate exposure and their correlations with childhood obesity and insulin resistance. Because of the growing fast food culture, endocrinal signaling thus could lead to perturbation of lipid and glucose homeostasis [10].

The molecular docking studies have revealed that the under-given important nuclear regulators in xenobiotic metabolism are more susceptible to strong interactions with phthalates or their metabolites as compared to their natural ligands [36–38]. Such unwanted cross-talks adversely affect the synthesis, secretion of hormones, and consequently the metabolism of lipid and glucose causing their impaired homeostasis.

- Estrogen and ketosteroid receptors (mineralocorticoids, glucocorticoids, progesterone, and androgens).
- Pregnane-X-receptor (PXR).
- Retinoid X α, β, or γ receptors (RXR).
- PPAR α, β, or γ subtypes.

The phthalates and their metabolites could bind more intensely to these receptors than their natural agonist thus act as EDCs because they impair normal molecular signaling processes by disturbing at least one of the links in web of communications. The circulating phthalate/metabolites reach the cytosol in the form of phthalate-protein complexes (by binding with fatty acid binding proteins (FABP) and liver (L-FABPs)). In digestive system, the phthalates bind with intestinal (I-FABP) which facilitate the transport of relatively more soluble phthalates from intestinal lumen to the sites of metabolism and distribution. The phthalate-HAS complexes also help in their transportation to hormone receptors. Afterwards, the phthalates are transferred from such complexes to afore-mentioned nuclear receptor proteins as co-activators and reside in nucleoplasm. These complexes further undergo hetero-dimerization to act as a transcription factor and bind to target genes responsible for xenobiotic metabolism and the biosynthesis of hormones resulting in their suppression or downregulation [39, 40].

General Health Impacts of Phthalates

In additions to above explained diseases caused by phthalates as EDCs, they have a lot many other deleterious health impacts in human beings. In males, the phthalate toxicity accounts for testicular dysgenesis syndrome characterized by infertility, decrease in sperm quality and its count, undescended testes, and testicular cancer

[41]. In additions to urine and blood samples, the phthalates can be detected in many other fluids in woman including follicular fluid, amniotic fluid, cord blood and saliva, thus suggests their capacity of penetration in whole body. This prevalence of phthalates in pregnant women could easily be transferred to fetus and cause impaired neurodevelopment, psychomotor and behavioral issues, decreased IQ and attention deficit, sex anomalies, and altered reproductive development [42, 43].

The alterations in the secretion levels of cytokines and phthalate-induced oxidative stress have been found to show association with allergies and asthma. The itchy rashes, hay fever, wheezing, bronchitis, and chest infections are the direct allergic responses of the high molecular weight phthalates [44, 45]. It has been considered that the phthalates could cause breast, gastrointestinal, liver, and skin cancers; however, no such solid clue has been available in literature.

Conclusion

Phthalates are ubiquitous in nature and human beings are constantly exposed to it in daily routine through food, inhalation, personal care products, clothing, and medication. Further, they can penetrate through almost all parts of body. The phthalates or their metabolites act as agonist or antagonist ligands and disrupt the chemical signaling of the endocrine hormones, thus are regarded as endocrine disrupting chemicals. The impaired endocrinal signaling disturbs the normal physiological functions in both genders including infants. Such abnormalities include sex anomalies, type II diabetes, overweight, and obesity. Considering the level of toxicity of phthalates, the safer alternatives should be adopted at the urgent possible to save the next generations from such deadly toxicants.

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Chapter 16
Bisphenol A as an EDC in Metabolic Disorders

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Abstract Bisphenol A (BPA) is a man-made chemical substance that is used in our daily life for the production of many plastic wares. In this chapter, sources of BPA exposure and its effects on human being have been summarized in detail. Many in vivo and in vitro studies show that BPA is considered as a toxic, mutagenic, carcinogenic, and endocrine disruptor. BPA has the ability to disrupt many metabolic pathways that alter the metabolism of carbohydrates and lipids that may lead to the development of metabolic disorders. BPA has its role in disturbing the functions of the liver and alters the production of insulin from β-cells of pancreatic islets. BPA also interferes with the utilization of glucose in the muscles and in the adipose tissues. It also disrupts the regulation of glucose metabolism in the central nervous system via the neuroendocrine system that leads to the intolerance of glucose and insulin which promotes metabolic syndrome. This discussion proves that BPA exposure is a major risk factor for metabolic diseases.

Keywords Bisphenol A · Metabolic disorder · Adipose tissues · Glucose metabolism

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Introduction

The occurrence of metabolic syndrome has been increased globally over the past years. The major cause of metabolic syndrome is the intake of high caloric diets, less exercise, and certain possible genetic predisposition. Some chemicals that are present in the environment and food play an important role in the expansion of these diseases by disrupting the normal physiology of endocrine systems [1]. Such chemicals are known as endocrine-disrupting chemicals (EDCs). Bisphenol A (BPA) is a man-made organic compound that is mainly present in many daily use products such as it is a constituent in the epoxy resins and polycarbonate plastics. There are chances for contamination of food products when this chemical comes into contact with food [2]. BPA is present in excess quantities that are primarily used for the production of epoxy resins and polycarbonate plastics. Polycarbonate plastics have been widely used in the food and drink containers such as water and infant bottles, safety equipment, compact disc, and many medical devices. Epoxy resins can be utilized as lacquers for the coating of many metal products. Exposure to BPA may also occur because it is present in many dental sealants and composites [3]. The population may be exposed to BPA through inhalation of dust and dermal contact [4].

BPA has the ability to bind with various receptors in the body such as androgen receptors, estrogen receptors, and peroxisome proliferator-activated receptors. The peroxisome proliferator-activated receptors are linked with hormones that are produced by the endocrine system and other systems of the body [5]. BPA exhibits the endocrine-disrupting activity and oxidative potential due to which it has a toxic effect on animals and human being [6]. BPA can disturb the functions of various kinds of hormones such as insulin, thyroxin, and leptin and be responsible for producing hepatotoxic, carcinogenic, immunotoxic, and mutagenic effects [7]. Recent studies show that BPA exposure to human beings leads to obesity, heart diseases, and diabetes [8].

From experimental studies, it has been concluded that BPA is less toxic to microorganisms that have the ability to transform BPA into its metabolites that has less toxic estrogenic effect than BPA [9]. Some organisms that have the ability to transform BPA into metabolites. These are used for removing this substance from the polluted environment [10]. Many investigations show that there is an interaction of mechanism between BPA and metabolic syndrome. BPA can cause a metabolic disturbance in adipocytes tissues and inflammation which leads to obesity [11]. Due to exposure of BPA to the human liver, it increases the production of glucose and decreases the synthesis of glycogen associated with a reduction in glucose oxidation and also disturbs the signals of insulin. When BPA is exposed to human muscle it causes a decrease in the utilization of glucose and insulin sensitivity [12].

Environmental Exposure

BPA is considered to be emitted into the atmosphere as a result of many industrial activities. It has been estimated that approximately 100 tons per year, BPA is released into the atmosphere. The concentration of BPA varies in the atmosphere [13]. A higher concentration of BPA has been found in the groundwater which is situated close to waste dumps that are contaminated with this kind of substances or there may be deposition of plastic deposits [14]. Mostly BPA is exposed to the human being through the food. BPA is present in the edibles and it can be exposed to the animal [15].

There are multiple routes for BPA exposure to human beings like transdermal, oral, and inhalation. The major sources of BPA exposure are packed food, thermal paper, baby toys, feeders, dust, healthcare equipment, dental materials, etc. (Fig. 16.1). There are different sources of BPA in the environment such as water, air, river, sea, and dust. These different sources are responsible for the exposure of BPA in the different concentrations to animals and human being as shown in Table 16.1. Sources of BPA and its concentration in the environment [16]. The widest source of exposure of BPA is food and beverages but exposure may occur through the skin after handling of thermal paper for a long interval of time. Mostly cashiers, a person who handles receipts for 40 h per week, are exposed to BPA via the skin [17].

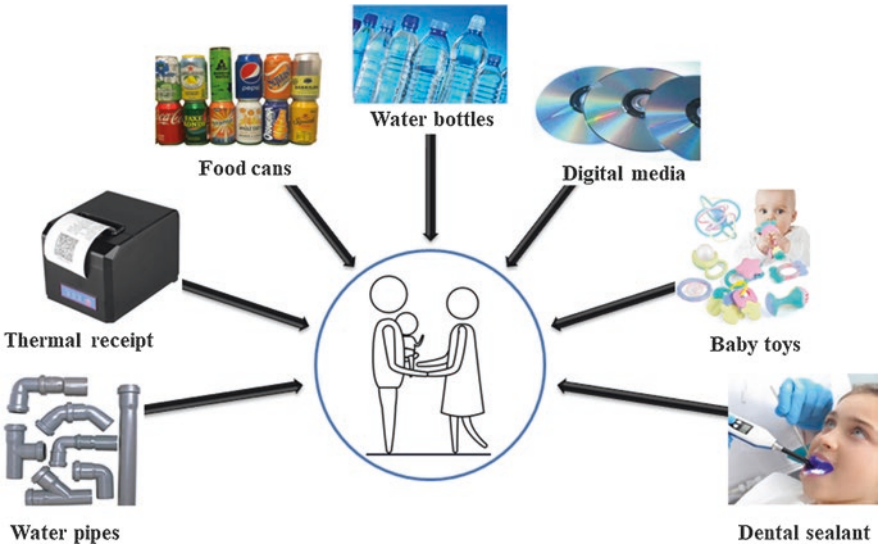

Fig. 16.1 Schematic representation of sources of BPA exposure to human beings

Table 16.1 Sources of BPA and its concentration in environment

Contamination sources of BPA	Concentration of BPA
Aquatic environment	8–21 ng/mL
Air	2–208 ng/m^3
Dust	0.8–10 μg/g
Thermal paper	54–79 μg/cm^2
Meats	17–602 ng/g
Fish	5–109 ng/g
Vegetable and fruits	9–76 ng/g
Beverages	1–18 ng/g
Dairy products	21–43 ng/g
Infants formula	0.1–13 ng/g
Cans	2–82 ppb
Plastics	0.2–26 ppb
Dental material	0.013–30 mg

Adapted from Ref. [16]
Abbreviations: *ppb* parts per billion, *ng* nanogram, *μg* microgram, *mg* milligram

Migration of BPA

The anthropogenicactivity is also responsible for the exposure of BPA in the environment. The major source for the occurrence of BPA is the generation, treatment and processing, degradation of many polymers such as epoxy resins and polycarbonates which release monomers of BPA into the atmosphere and many food products. BPA can be released from polycarbonate by the process of diffusion or hydrolysis. If there is a low pH of the solution of polycarbonate, then the rate of release of BPA is increased but cation has no effect on the polycarbonate hydrolysis [18]. The rate of release of BPA from the polycarbonate bottles is increased by increasing the temperature which enhances the process of hydrolysis [19]. The food is also exposed to BPA when packed in containers usually tin having lacquers coating. These lacquers are composed of epoxy resins which contain BPA diglycidyl ether as an essential component [20]. The purpose of coating is to prevent the corrosion of the metal and protection of the food from the contamination of metal which may occur during the process of sterilization and storage. The epoxy resins present in the container are also responsible for the release of BPA and its release depends upon temperature during the pasteurization of the tin canned food. The released concentration of the BPA from lacquers also determines the extent of the polymerization of epoxy resins [21].

BPA Effect on Obesity

Previous investigations show that some chemicals have an effect on the endocrine system and disturb the endocrine balance which is the major factor for the development of obesity. Endocrine-disrupting chemicals can disturb the functions of fat

tissues that contain alpha and beta receptors. BPA can interfere in the activity of aromatase, regulators of lipogenesis, lipoprotein lipase, and level of hormones in fat tissues that are very crucial for balancing the weight of the body [22]. There is a link between exposure to BPA and an increase in body weight [23]. Previous studies show that when low doses of BPA are exposed to mice in the perinatal period then the volume of adipocytes is increased as a result the body weight increased. The concentration of BPA in urine is mainly associated with obesity in the children and adolescent but this association is also correlated with food consumption that contains a high level of BPA in adipose tissues [24]. New research concluded that BPA is considered as obesogens in the environment which is responsible for epidemic obesity in the entire world [25]. BPA causes disruption in the functioning of the endocrine system and also responsible for modulation in expression of genes by hypomethylation of the gene promoter which leads to cancer, heart diseases, and obesity [26]. BPA contributes to the metabolic diseases by the disruption in the glucose homeostasis. Due to the increased level of BPA, the risk of diabetes is high irrespective of the age, sex, body mass index, and level of serum cholesterol [27].

BPA Effect on the Cardiovascular System

Cardiovascular disease is nowadays becoming a major health problem and a significant contributor to mortality and morbidity rate. BPA is considered a major contributor to cardiovascular diseases including angina, hypertension, coronary artery disease, heart attack, and peripheral artery disease. BPA may cause cardiovascular disease due to genetic, physiological, and pathophysiological variations [28]. The investigations have shown that a low dose of BPA has an effect on cardiac rhythm in the adult rat's heart [29]. BPA is also responsible for disturbing the normal function of the cardiovascular system. National health and nutritional examination survey conducted research which explains that there is an association between the concentration of BPA in the urine and the coronary heart disease [30]. There is also an association between the concentration of BPA in the urine and peripheral arterial disease. There is also an association between the urinary concentration of BPA and hypertension [31]. Various studies have also exposed the mechanism of BPA on the heart. BPA has a pro-arrhythmic effect in the heart cells of the female rat by the alteration in the handling of calcium in the myocytes [32]. The physiology of cardiac cells, electrical excitation, and relaxation mechanism depend upon the handling of the calcium ions. If any abnormality occurs in the handling of calcium ions, then cardiac arrhythmogenesis occurs [33]. Due to exposure of BPA to female myocytes rat, an increase in the reuptake and release of calcium ions in the sarcoplasmic reticulum occur.

BPA affect on cardiac myocytes by two signaling pathways such as protein kinase A and calcium-dependent protein kinase II. As a result, the production of cAMP increases due to activation of protein kinase A and phosphorylation of the

ryanodine receptor also occurs. BPA also causes an increase in phospholipase C activation, triphosphoinositol (IP_3) production, and release of calcium-mediated by IP_3 receptor. Phosphorylation of the ryanodine receptor increases the leakage of calcium from sarcoplasmic reticulum due to the opening of calcium channels. Activation of calcium-dependent protein kinase II causes the phosphorylation of phospholamban which inhibits the calcium release from endoplasmic reticulum Ca^{2+}-ATPase and increases the uptake. These pathways cause arrhythmogenesis in myocytes [28].

BPA Effect on the Liver

The liver plays a key role in the regulation of glucose metabolism via hepatic glucose production. In addition, the liver is the main organ responsible for the detoxification of chemicals that are present in the whole body as the center of the metabolism of toxic substances, drugs, xenobiotics, and environmental hormones. BPA, belonging to environmental xenobiotic contaminants, reaches the liver where it gets metabolized [34]. BPA has the ability to damage the cells in the liver due to oxidative stress. BPA has significantly reduced the level of antioxidant enzymes and glutathione levels due to a reduction in the activities of glutathione-S-transferase. Due to high exposure of BPA, increased sufficiently the concentration of the enzymes in the liver and also increased the activity of the antioxidant genes in the tissues of the liver. The research has proved that reactive oxygen species increased due to BPA exposure and also causes a reduction in the expression of genes, ultimately responsible for hepatotoxicity [6]. The low concentration of BPA can also cause hepatotoxicity which may be due to disturbance in the function of the mitochondria, abnormality in the production of reactive oxygen species, hyperpolarization of the mitochondrial membrane, oxidation of lipids, and release of the cytokines [35]. Another study also shows that oxidation of the lipids decreases the level of glutathione peroxidase, pro-inflammatory cytokines including the tumor necrosis factor and interleukin 6. Exposure of BPA in very low concentration has also an effect on decreasing the oxygen level, production of ATP, and disturbs the function of the mitochondria that is present in the liver cells [36].

BPA Effect on the Immune System

BPA has an effect on the estrogenic receptors due to which it has the ability to induce modulation in the immune system functions. BPA has also the ability to bind with aryl hydrocarbon receptor and peroxisome proliferator-activated receptor. BPA has the capability to stimulate and inhibit the activity of the cells in the immune system [37]. Due to exposure of BPA, the amount of T lymphocytes is increased and as a result, the level of interferon increases while interleukin level is decreased [38].

BPA has the capability to modulate the B cell proliferation and production of cytokines and some antibodies [39]. BPA is responsible for the non-specific immune defense mechanism. BPA produces lymphocytes with a higher concentration of immunoglobulin A and also immunoglobulin G 2a [40]. Studies also show that female mice exposed to BPA have more susceptibility for infection caused by the influenza virus which causes a modulation in the immune system [41]. National Health and Nutrition Examination Survey shows that the concentration of BPA is associated with cytomegalovirus antibody titers and a negative impact on the immune functions of the human [42].

BPA Effect on DNA

BPA has the ability to damage DNA in the eukaryotic cell [25]. BPA has the ability to cause modulation in histone phosphorylation which leads to genotoxicity in intestinal cells, hepatoma cell and renal cell line of the human. But no genotoxic effect is produced in the human [43]. Some studies show that BPA metabolites are responsible for inducing the genotoxic effect. The metabolites of BPA such as BPA-quinone has the ability to bind with DNA by a covalent bond [44]. Another study also shows that BPA has the ability to bind with DNA and form an adduct with nucleotide deoxyguanosine which proves that BPA acts as DNA mutagen [45].

BPA Effect on Adipocytes

Recent studies show that fat tissues produce hormones that are responsible for regulating the body metabolism and many processes. Fat cells produce leptin that has an influence on the body weight by affecting the hypothalamus. It also has an effect on the reproductive processes by influencing the mechanism of gonadotropins hormone [46]. Adiponectin is a hormone that is produced by the adipocytes involved in the regulation of glucose intake in the cells [47]. An extensive number of chemicals and growth factors cause modulation in the function of various hormones such as insulin, glucocorticoids, catecholamines, thyroid hormone, estradiol, and other chemical substances that have effect on estrogen activity [48]. Lipoprotein is a major enzyme that is involved in the regulation of lipids. The lipoprotein is regulated by estrogen [49].

BPA and estradiol have equal potency to bind with the receptors that are present on the cell membrane and start the cascade of the reactions. BPA has been considered as selective estrogen receptor modulator [22].

BPA is responsible for increasing the activity of lipoprotein lipase and causes accumulation of triacylglycerol. It happens due to the presence of larger droplets of lipids in the differentiated cells [50]. BPA and insulin have the capability to interact synergistically for the acceleration of this mechanism. BPA is also responsible for

the activation of glucose transporter which enhances the uptake of glucose in the adipocytes [51]. Another study shows that perinatal exposure of BPA in male rat offspring in later life reduces the gene expression and production of adiponectin. Exposure to a high concentration of BPA causes metabolic dysfunction [52]. Exposure of low concentration of BPA to human adipocytes in vitro causes dysregulation of the functions of adipocytes by impairing the utilization of glucose-stimulated by insulin and pathway of insulin signaling [51].

Impairment in Glucose Metabolism

BPA has the potential to exhibit its role as an obesogen and diabetogenic. Only diet and lifestyles are not sufficient to elaborate on the incidence of obesity. Many endocrine-disrupting chemicals can disturb the homeostasis of glucose in the various organs such as the liver, pancreas, adipocytes, and neuroendocrine cells [53]. BPA influences the glucose homeostasis in liver, adipose tissues, skeletal muscles, pancreas, and central nervous system.

Impairment in Insulin Secretion from Pancreatic Islets

The pancreas produces hormones, insulin, and glucagon, for the regulation of glucose homeostasis [54]. B-cells of pancreatic islets are responsible for producing and releasing the insulin while α cells of pancreatic islets are responsible for producing and releasing of glucagon. Any abnormality in pancreatic function leads to the disruption in the production and release of hormones; insulin and glucagon, which may lead to the development of T2DM and insulin resistance that are the major contributing factors for obesity and metabolic syndrome [55]. Estrogen has also a role in maintaining the function of the pancreas by binding with the estrogen receptor that is present on the pancreas. It has the potential for maintaining the functions of β-cells and the sensitivity of insulin. If there is a low level of estrogen in the body, then intolerance of glucose and resistance to insulin is developed in the body [54]. BPA is considered a xenoestrogen substance, which mimics the action of estrogen in the pancreatic cells. BPA is responsible for the overproduction of insulin as 17-β estradiol by binding with estrogen receptor and activating extracellular signaling kinase [56]. BPA exposure cause fasting hyperglycemia, hyperinsulinemia, and intolerance of glucose in animals [57]. Another study shows that BPA has an opposite effect on the production of insulin when using the insulinoma cells of a rat as β-cells. BPA exposure induced apoptosis in the rat insulinoma cells, reduction in the viability of cells that are triggered by defects in mitochondria and decreased insulin production and secretion by stimulation of glucose [58].

Effects of BPA on Glucose Uptake

Balancing the homeostasis of glucose in the body is a key process for maintaining the metabolism of the whole body from birth to onwards. But this is a very complicated process that is balanced by the production and utilization of glucose by various tissues that participate in the regulation of the metabolism. Skeletal muscles have an important role in maintaining the glucose concentration in the systemic circulation because glucose uptake occurs by skeletal muscles in response to insulin. Utilization and uptake of glucose usually occur by glucose transporter (GLUT4) via the involvement of the receptor of insulin and Akt signaling [59]. Insulin not only maintains the level of glucose but also increases the utilization of glucose mostly in muscles and hepatocytes and decreases the production of glucose by the hepatic cells [60]. Recent studies show that exposure of BPA to pregnant mice and adult male offspring impairs both insulin and glucose tolerance via inhibiting the activation of the Akt signaling pathway. As a result, it decreases the sensitivity of peripheral insulin [61]. Another study shows that exposure of BPA to adult male rats causes the down-regulation of receptors of insulin and Akt phosphorylation and protein expression for glucose transporters in membrane and cytosol [62].

Effect of BPA on the Neuroendocrine System

BPA has an influence on the differentiation of sex in the brain of rodents, development of cortical in the mice, hippocampus on the rat, midbrain dopamine of neurons, and synapses of the hippocampal spine [63]. The feeding behavior and expenditure of energy are regulated by the central nervous system via the hypothalamus. Both of these functions are affected by many peripheral signals such as insulin, glucocorticoids, glucose, leptin, thyroid, and steroid hormone. The melanocortin system of the hypothalamus, situated in the hypothalamic arcuate nucleus, is crucial for controlling the appetite and homeostasis of energy. The pro-opiomelanocortin (POMC) neurons enhance satiety that is associated with the utilization of glucose by peripheral tissues and inhibition of glucose production by the liver. The Neuropeptide Y/Agouti-related peptide (NPY/AgRP) neurons are activated in the fasting condition or during the restriction of calorie intake to increase the demand for food intake, utilization of stored fat, and production of glucose in the liver. Any abnormality in this system leads to metabolic disorders such as obesity and T2DM [64].

It has been demonstrated that there is communication between the signals of estrogen and leptin in the hypothalamus during the regulation of feeding [65]. It has been assumed that exposure to BPA can cause alteration in the homeostasis of glucose. BPA has an effect on the activity of POMC and NPY/AgRP neurons. The study suggested that exposure of BPA in early stage of life induces obesity in mice. This exposure of BPA may lead to a reduction in signal from POMC fiber to paraventricular nucleus in hypothalamus and increase the expression NPY/AgRP peptides in

arcuate nucleus. Female mice exposed to a high-fat diet, will show a decrease in the expression of POMC gene in arcuate nucleus upon exposure to high concentration of BPA. Early life exposure of BPA to both male and female mice causes impairment for the tolerance of glucose [66].

Conclusion

BPA is a synthetic organic compound and one of the most vulnerable endocrine-disrupting chemicals that is being used in many products of daily uses. Food is the most common source of BPA exposure. It has been proved that BPA exposed to humans can cause interaction with many receptors such as estrogen, aryl hydrocarbon, androgen, and peroxisome proliferator-activated receptors and change the function of leptin, insulin, adiponectin, thyroxin, and other hormones that are involved in the maintaining of the immune and nervous system. BPA induces the production of oxidative stress, impairs signaling of cell and changes in DNA due to inhibition of methylation of DNA. BPA also enhances the risk of coronary heart diseases and metabolic disorders.

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Chapter 17
Role of Pesticides as EDCs in Metabolic Disorders

Shagufta Kamal, Muhammad Junaid, Ismat Bibi, Saima Rehman, Kanwal Rehman, and Muhammad Sajid Hamid Akash

Abstract Pesticides or environmental chemicals have superiority of speed control in conditions of massive pest outbreak against biological and cultural control practices which remained active for extended span. Nevertheless, there are severe ecological and environmental problems with reliance on pesticides. Persistence of pesticides in the food chain and the development of resistance in pests are the two main challenges. The unprotected populations present deleterious health effects. Chronic effects of these environmental contaminants are neurotoxicity, carcinogenesis, developmental and reproductive disorders. In this chapter we tried to summarize the need of pesticides, history, methods of exposure. The chapter also focuses on the metabolic disorders, interaction of recalcitrant with complex enzyme systems and influence on genders. Precautionary measures are also discussed in details.

Keywords Environmental chemicals · Deleterious health effects · Carcinogenicity · Neurotoxicity

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Introduction

The worldwide population is projected to increase to 9 billion by 2050. To accommodate this increase, food production will necessarily need to increase as well. However, new agricultural land is limited, so sustainable production and increasing productivity of existing agricultural land is an important aspect to addressing global food security [1]. The food production per capita can be increased by enhancing the yield of crops through proper management of soil and water and with the usage of agrochemicals. Agrochemicals include two types of compounds; fertilizers and pesticides. However, with the increased production of food through immense use of fertilizers has contaminated the aqua life and also caused serious consumption problems in humans [2].

In the last few decades pesticides also have provided great assistance by reducing significant lose, enhancing food production as well as the protection of cattle and protect human from numerous contagions. Lots of chemical are operated in the modern society; some of these recalcitrants accidently harm humans as well as our environment. A Swiss chemist Paul Hermann Muller received Nobel on discovery of 1,1′-(2,2,2-trichloroethylidene) bis (4-chlorobenzene) (DDT), highly efficient poison active against numerous arthropods in 1948. Due to potential harm to human and on the basis of various ecological considerations, the use of this potent pesticide was banned by Sweden in 1970, and subsequently in 1972 followed by many other countries. A number of pesticides used in agricultural areas have contributed to serious environmental pollution leading to toxicity in human. In few years the growth in pesticides usage has increased dramatically that acted as poisons in killing not only targeted species but also causing serious damage to non-targeted species. These poisons mostly reside in food or water and can also be found in our surrounding environments such as in lawn sprays, households bugs sprays, leading to direct exposure to humans that cause toxic effects by accumulating in tissues [3]. Pesticides have great magnitude of translocation even in areas where these pesticides are used in very minute amount. Pesticides have dangerous concern not only in chemical industry, forestry and agricultural applications, wildlife and domestic uses but also toxic to every person who wants to get food at reasonable price [4].

In last few years knowledge about pesticides as endocrine-disrupting chemicals (EDCs) has been increasing speedily. There is growing data of literature about these chemicals that act as EDCs by putting toxic effects on human health. EDCs are that class of chemicals that targets the hormonal controls of body by interfering the production, release, action, metabolism, and transport of naturally occurring chemicals. Mostly pesticides target the hormonal signaling pathways and neuroendocrine system also causing oxidative stress leading to various metabolic diseases [5].

The current chapter aims to highlight the role of pesticides as endocrine-disrupting chemicals (EDCs) as well as metabolic disorder chemicals (MDCs). This chapter also focuses on the major chronic health effects associated with the exposure of pesticides; given the fact that adverse health effects are extensively analyzed with respect to the latest literature. Emphasis is also given to precautionary measures.

These health effects reveal that some urgent alternating solutions are the need of time.

Historical Perspective

The history of pesticide usage or manufacturing is dated back to classical Greece and Rome approximately 79 AD. More information became available in the sixteenth century. The modern synthetic pesticides were developed around World War II when the insecticidal potential of DDT was discovered in Switzerland and insecticidal organophosphates were developed in Germany. At about the same time work was in progress in Britain which led to the commercial production of herbicide of the phenoxy alkanoic acid group. In 1945 the first soil-acting carbamate herbicides were discovered by British workers and the organochlorine insecticide, chlordane, was introduced in the USA and in Germany. Shortly afterwards, the insecticidal carbamates were developed in Switzerland. In 1950–1955, herbicidal urea derivatives were developed in the USA, the fungicide captan and glyodin appeared, and malathion was introduced. Between 1955 and 1960, newcomers included herbicidal triazines (Switzerland) and quaternary ammonium herbicides (Britain). Relatively few new groups of crop protection compounds have been discovered since then. As mentioned above, post-World War II era saw a boom in the synthetic pesticide production and thousands new compounds had been screened for pesticidal activity [6]. The discovery of DDT and analogues was thought to be miracle and a permanent solution to pest problem. However, Rachel Carson's "Silent Spring" in 1962 was the first to draw our attention towards the retention and built-up of persistent organochlorine pesticides in the food chain. "Silent Spring" has become synonymous with the massive poisoning of birds caused by DDT, from eagles to hawks to songbirds. While DDT is banned in many countries and some affected bird populations are now beginning to recover, hundreds of bird species continue to be threatened by other pesticides [7].

Classification of Pesticides

Pesticide is a broader term; it may be used as household dis-infectants, wood preservatives, fungicide, herbicide, rodenticide, and insecticide. Having different identities, physicochemical properties, pesticides can be classified (Fig. 17.1) on the basis of (1) chemical composition (2) mode of action (3) targeted species [8]. Classification on the basis of their chemical is rather complex yet it gives clue about physicochemical characteristics of pesticides. These characteristics help to decide the mode, precautionary measurements, and application rates of pesticides [9]. Generally, pesticides are mostly organic in nature having two basic groups, i.e., halogenated hydrocarbons and aromatic hydrocarbons [10]. Non-systemic pesticides

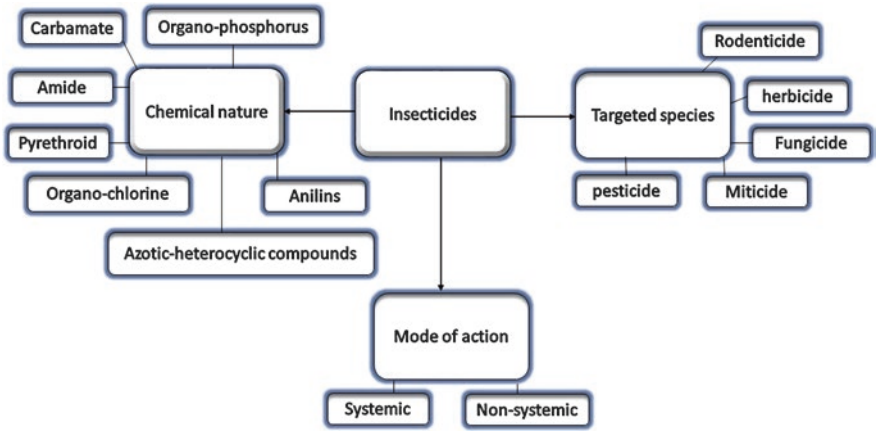


Fig. 17.1 Classification of pesticides

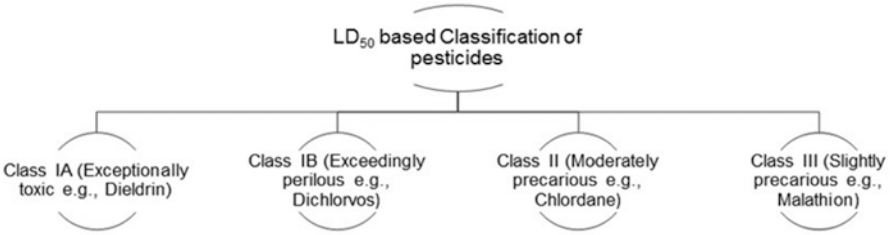


Fig. 17.2 Classification of pesticides on the basis of spectrum

treat plants without penetrating the vascular system, e.g., diquat dibromide, etc. [11]. Vegetable, fruit, and soil pests can be removed by fumigants. Some pesticides like acaricide is a well-known insectoid but it may have ability to control mites, nematodes while herbicide 2,4-D is a potent plant growth regulator [12]. Pesticides may be classified (Fig. 17.2) as narrow- and broad-spectrum pesticides such as chlorpyrifos, chlordane, etc. Pesticides are also classified into wettable powder, dusts, emulsifiable concentrates, and baits on the basis of their formulations. These can also be classified on the basis of their synthetic era like DDT group, hexachlorocyclohexane, cyclodienes, organophosphates, and pyrethroids, etc (Table 17.1). Classification of pesticides on the basis of their toxicity [13]. National Toxicology Program in 2013 reported the link of pesticides with obesity and diabetes and classified pesticides into five groups (Table 17.2).

Active ingredients of pesticides are the representative of their form, odor, color and also help to identify pesticides after severe injury in the areas where facility of identification is not available such as surflan possesses opaque orange liquid appearance with mild aromatic order and cyproconazole is a beige colored crystalline powder without order, etc. [14]. Potent pesticides should have $K_{OC} < 500$, solubility <30 ppm, volatile having vapor pressure $< 10^{-5}$ atm, having -Ve charge if pKa < 3,

Table 17.1 Classification of pesticides on the basis of their toxicity

S. no.	Classes	Examples	Ref.
1	Persistent organic pollutants	Polychlorinated biphenyls, polychlorinated naphthalenes, polychlorinated dibenzofurans, polybrominated diphenyl ethers, dichloro-di-phenyl-tri-chloroethane	[130]
2	Non-persistent organic pollutants	Bisphenol A, atrazine	[131]
3	Metals	Arsenic, Di(2-ethylhexyl) phthalate	[132]
4	Drugs	Pharmaceuticals	[133]

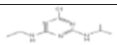
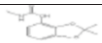
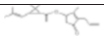
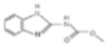
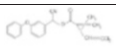
neutral if pKa < 10, volatility, mobility, and solubility should be influenced by pH if both pH and pKa values are close enough [15].

Use of Pesticides in Crops

One-third food crops of the world have been ruined during maturation, cultivation, and storage by pest attack. This loss become very severe in developing nations [16]. However, tillage has to face rising global demand for feed, fiber, food, and other bio-based commodities like biofuels, etc. These global demands would be fulfilled at the expanse of natural habitats of wildlife, natural enemies of crop pests, forests due to resources of extra-agricultural land are very limited. Disposed these shortcomings, raising productivity, unceasing presentation on the available land, and averting the superfluous loss along the entire length of food chain is by far more competently option. The most advantageous use of combination technology is the need of time to improve agriculture productivity and to improve the human's living standard by decreasing prices of food stuffs. The major challenge facing agriculture production is the loss of yield due to attacks of pathogens, weeds, and pests [17]. Analysis of cost-benefits regarding the pesticides practice is an important tool to appraise policy decisions. The most difficult challenge for policy makers is to achieve a balance between risks and benefits of pesticides on the community. Pesticides due to unavailability of universally competitive alternatives are playing a major role in counteracting the pest to increase food productivity.

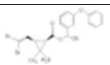
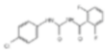
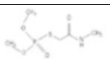
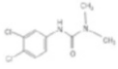
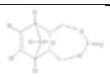
The use of some pesticides like organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs), etc., in Asian developing countries has extensively been increased during the last few decades. According to available data, China (1950–1980) produced approximately 400Ktons of $C_{14}H_9Cl_5$ (dichlorodiphenyltrichloroethane; DDT) and 4.9Mtons of hexachlorohexane (HCHs) that constituted about 20% and 33% of world's total production [18]. Annual consumption of pesticides in countries like India, China, Vietnam, etc., is about 85,000 metric tons among which major pesticides (approximately 70%) used are malathion, DDTs, and HCHs [19]. In recent few years DDTs are extensively used for both agricultural

Table 17.2 Sources and methods of different pesticides exposure

S. no.	Pesticides	Structure	Issue date	Ban date	Exposure to human	Source	Ref.
1	Atrazine		1958	1991	Inhalation, contaminated food, skin contact	Herbicides, pharmaceuticals	[36]
2	Bendiocarb		1971	1991	Inhalation, contaminated food, skin contact	Carbamate insecticides used in agricultures and in pest killing	[37]
3	Benomyl		1968	2004	Skin contact	Benzimidazole carbamic acid, methyl ester (BCM)	[38]
4	Bioallethrin		1969	NA	Inhalation	Household pest insects	[119]
5	Captan		1951	2009	Contaminated fruits, vegetables, and ornamentals	Fungicide, cosmetics and pharmaceuticals	[39]
6	Carbaryl		1953	2001	Skin contact, inhalation or ingestion	Agricultural insecticides, pest killing chemicals, household settings	[40]
7	Carbendazim		1973	2017	Oral ingestion, inhalation and dermal contact, contaminated water and food	Veterinary medicine, livestock	[41]
8	Carbofuran		1969	2009	Contaminated meat or milk, dermal, ingestion	Exposed goats, carbamate pesticides	[134]
9	Chlorothalonil		1966	2020	Contact with skin and eyes, oral	Contaminated food, vegetables, golf courses and lawns	[135]
10	Chlordane		1948	1988	Inhalation, contaminated land	Contaminated land, house pesticides, used on corn and citrus crops	[136]
11	Chlordecone		1958	2009	Inhalation, eye contact	Fungicide and acaricide	[137]
12	Chlorfenvinphos		1963	1991	Inhalation, contact with skin, contaminated agricultural products	Pesticide application, dairy farming, cattle or sheep holding, or poultry production	[138]
13	Chlorpyrifos methyl		1965	2018	Inhalation, skin contact	Insecticide, acaricide, miticide	[139]
14	Cypermethrin		1977	2009	Skin contact or ingestion	veterinary medicine, agriculture to control ectoparasites	[140]
15	Cyproconazole		1994	2021	Inhalation, dermal contact	Fungicides, use for preservation of crops trees, fruits and wood	[141]
16	DDT and metabolites		1945	1970	Inhalation and dermal contact	Insecticides, domestic pests' killers' chemicals	[142]

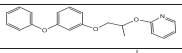
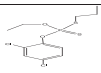
(continued)

Table 17.2 (continued)

17	Deltamethrin		1974	2007	Inhalation, skin contact, contaminated food	Insecticides, Bed bugs and mosquitos' killers' chemicals	[143]
18	Diazinon		1952	2004	Inhalation, skin contact, contaminated food	Domestic insecticides	[144]
19	Dichlorvos		1961	1998	Inhalation and dermal contact	Domestic insecticides, household pests, in public health	[145]
20	Dicofol		1957	1989	Inhalation and dermal contact	Foliar spray on agricultural crops and ornamentals	[123]
21	Dieldrin		1948	1970	Oral ingestion, inhalation, dermal contact	Foliar spray on agricultural crops and ornamentals	[146]
22	Diflubenzuron		1975	1995	Inhalation of dust particles, dermal contact, ingestion of contaminated food	Forest management and on field crops	[147]
23	Dimethoate		1950	2016	Ingestion and skin contact	Contaminated fruits, insecticides used in home garden and agricultural areas	[148]
24	Diuron		1954	2012	Oral ingestion, inhalation and dermal contact	Residual herbicide and algaecide	[149]
25	Endosulfan		1954	2011	Ingestion of contaminated food, skin contact	Insecticide and acaricide	[150]
26	Endrin		1950	1984	Inhalation, contaminated water, agricultural areas	Pesticide to control insects, rodents, and birds	[151]
27	Epoxiconazole		1993	2000	Skin contact, inhalation, oral	Pharmaceuticals, fungicides	[151]
28	Fenarimol		1984	2012	Dermal adsorption, inhalation	Ornamental plants, trees, lawns, contaminated food	[152]
29	Fenitrothion		1959	2006	Oral, inhalation	Agricultural areas, herbicides	[153]
30	Nitrofen		1966	1996	Inhalation, contaminated water, agricultural areas	Agricultural areas, herbicides	[154]
31	Acephate		1973		Skin contact, inhalation,	Domestic insecticides, pharmaceuticals	[155]
32	Acetochlor		1958	2013	Oral, skin contact	Agricultural areas, herbicides	[156]
33	Alachlor		1969	1985	Inhalation, dermal contact	Agricultural areas, herbicides	[157]

(continued)

Table 17.2 (continued)

34	Aldrin		1950	1987	Inhalation, dermal contact	Domestic insecticides	[158]
35	Vinclozolin		1981	2006	Inhalation, dermal contact	Irrigation system and horticulture	[159]
36	Trifluralin		1986	2015	Ocular, inhalation, dermal contact	Agricultural and non-agricultural applications	[160]
37	Triadimenol		1984	NA	Oral, ocular, inhalation, ingestion, dermal	Agriculture	[161]
38	Toxaphene		Late 1960s and 1970s	1990	Ingestion, inhalation, dermal	Agriculture	[162]
39	Tribenuron-methyl		1986	2015	Ocular, inhalation, and dermal	Agricultural and non-agricultural applications	[163]
40	Tolchlofos-methyl		1983	NA	Occupational and aquatic life inhalation	Agriculture and plant production	[164]
41	Tetramethrin		1968	NA	Dermal, ocular, ingestion, inhalation	Domestic application	[165]
42	Tebuconazole		1994	NA	Oral, inhalation, dermal	Agricultural and non-agricultural	[165]
43	Sumithrin		1976	2006	Dermal, ingestion, inhalation	Domestic, commercial, horticulture, pet products, and mosquito control programs.	[166]
44	Simazine		1957	NA	Inhalation, ingestion, dermal	Agriculture, horticulture and industrial	[167]
45	Resmethrin		1967	NA	Dermal, ocular, inhalation, ingestion	Agricultural, domestic, industrial	[168]
46	Pyripyroxifen		1996	NA	Ocular, dermal ingestion, inhalation	Agriculture and domestic application	[169]
47	Prothiophos		1982	NA	Inhalation, dermal, ocular	Agriculture applications	[170]
48	Propoxur		1959	NA	Inhalation, ingestion, dermal	Agriculture, turf, forestry, domestic	[171]
49	Propazine		1997	2004	Oral, ingestion, ocular, dermal	Agriculture applications	[172]
50	Propanil		1961	NA	Ocular, dermal contact	Agriculture applications	[173]
51	Propamocarb		1984	NA	Dermal, inhalation	Agriculture applications	[174]
52	Procymidone		NA	2007	Dermal contact, inhalation	Horticulture uses	[175]
53	Propoxur		1959	NA	Inhalation, ingestion, dermal	Agriculture, turf, forestry, and domestic applications	[176]
54	Propiconazole		1987	NA	Ocular, dermal contact	Agriculture applications	[172]

commodities and vector control processes in Asian developing countries [20]. Agriculture is totally dependent on chemical pesticides for controlling insects to enhance productivity in developing countries. Total consumption of pesticides in developing countries is approximately 80% of overall world production according to the reports of World Health Organization [21]. Therefore, farmers in these countries are at great risk of chronic or acute health effects [22]. While the use of pesticide in Pakistan had been started since 1954 and up till now six different types of

rodenticides, 30 types of fungicides, 39 weedicides, and more than 108 different types of insecticides have been used between 1980s and 1990 [23]. Some of these pesticides are reported to have endocrine-disrupting properties [24]. GDP for agriculture in India is 130 billion USD which share 19% of GDP in total economy [25]. Among different type of pesticides, organochlorine (about 40%) is predominately used in India [26].

The applications of pesticides for residential indoor as well as outdoor in developed countries like USA are also widely spread as survey of four metropolitan areas indicated 94% use of insecticides in approximately 513 homes. Whereas telephonic survey indicated that pesticide use in the 238 homes of Missouri is approximately 98% per annum [27]. USA is among one of the biggest consumers of polybrominated diphenyl ethers (PBDE) who use 45% of total world consumption. Different forms of polybrominated diphenyl ethers (PBDEs) like penta-, octa-, and deca-, penta brominated diphenyl ethers are usually applied on soft products, i.e., chairs, sofas, etc., hence can easily be released and more susceptible to humans as endocrine-disrupting chemical. Therefore, general public of USA and Canada are facing greater threats due to more bioavailable nature of penta-BDE than deca-BDE. To date, highest concentration of penta-BDE has been reported from the blood and milk samples of US population [28]. Approximately 6.6 and 12.0 kg ha^{-1} is a total use of pesticide in Korea and Japan [29]. Immunological effects by comparing N_2O production and cytotoxic analysis of lipopolysaccharide stimulated macrophage cell line indicated that 21 different types of EDCs are present in Korean ecosystems. Relevant ministries of Korea after mid- or long- term research plans (1999) established safety managements of these EDCs (between 2007 and 2011) in all their respective ministries and special public website covering all information regarding

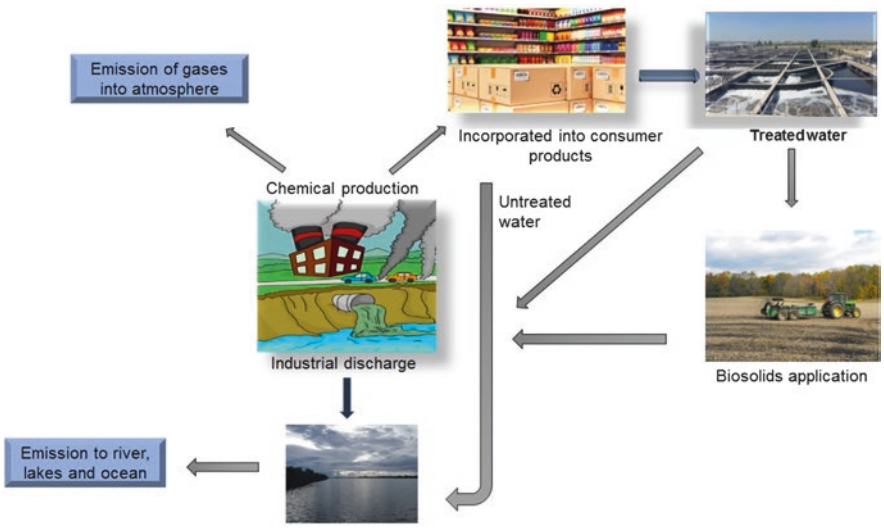


Fig. 17.3 Several ways for the exposure of pesticides to humans

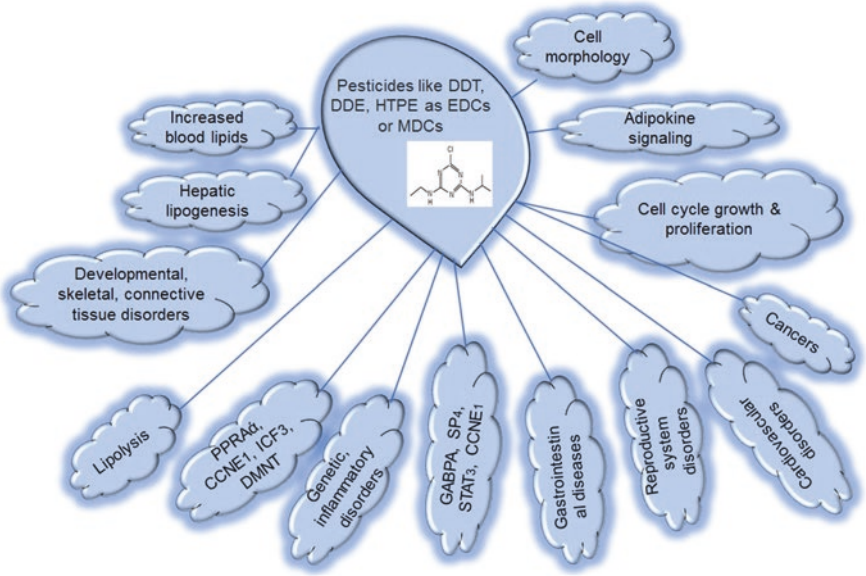


Fig. 17.4 Effect of pesticides on human health

EDCs [30]. Literature reported that concentration of PCBs is much in the samples from open ocean, terrestrial, and coastal environments than open seas in Japan [31]. Japan is badly affected by dioxin ($C_4H_4O_2$; well-known POPs), methylmercury $[CH_3Hg]^+$, PCB, cadmium (Cd), etc. Govt. of Japan constitute Three major ministries of Japan 1. Ministry of Environments 2. Ministry of Health Labor and Welfare 3. Ministry of Economy, Trade and Industry established endocrine disruptive effect (EDE) subcommittee to deal with pesticide residues in food, water, and air [32].

Lakes, rivers, agricultural chemicals, and sewage effluents are the main source of these EDCs in North America and Europe [33]. However, in developing countries like Asia or Africa industrial effluents and unconstrained domestic use of pesticides endow tremendously to elevated levels in aquatic habitats [6]. Many synthetic pesticides, listed as EDCs in developing or developed countries are adopted or misused in South Africa due to rapid industrialization [34]. Therefore, people and wildlife in South Africa are facing severe consequences of health [35]. Waters of Antarctic and Arctic oceans have huge distributions of PCBs and organochlorine pesticides [36]. US TTIP negotiators insisted on many pesticides containing EDCs which were banned in 2013. According to the criteria of European Commission many EDCs including toiletries, insecticides, pesticides linked to disorders of children, cancers, and birth defects are banned in 2014. After publishing the consequences of EDCs on male reproductive system by Copenhagen based Nordic Council reports, USA designated 59 M to 1.18 billion Euros for health system [37].

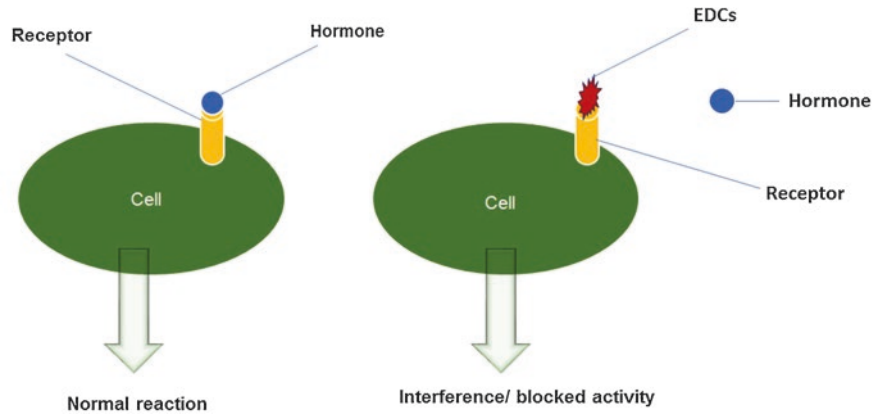


Fig. 17.5 Role of pesticide as EDCs

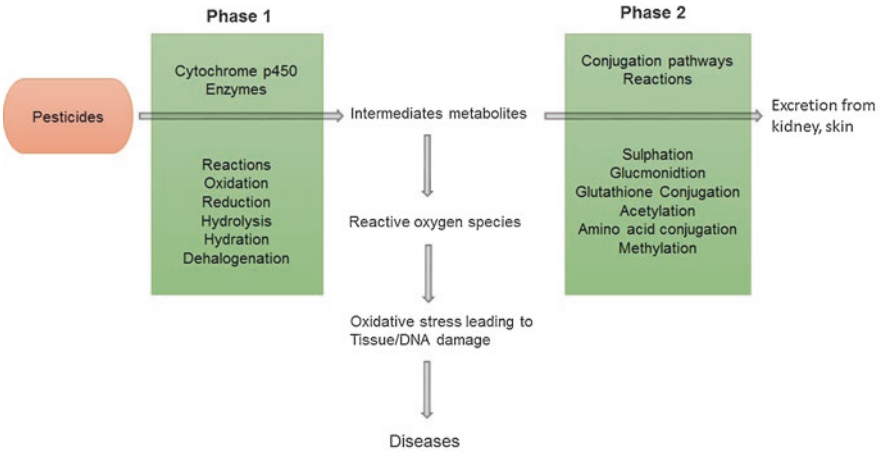


Fig. 17.6 Schematic representation of metabolism of pesticides

Human Exposure to Pesticides

Huge amounts of pesticides natural or synthetic other than POPs are designated as endocrine-disrupting chemicals (EDCs). These pesticides may also undergo different transformation processes resulting into the formation of different types of EDCs present in heterogeneous classes. Once these pesticides released into environment, they are aggravated. Some pesticides have shorter half-lives but unfortunately, they are continuously releasing into the environment as agricultural runoff or urban environments, therefore should be present in high amounts surrounding their sources (Fig. 17.3). Exposure to agricultural drift, dietary exposure to pesticide residues, i.e., contaminated meat, fish, vegetable, rice, etc., are the main sources for their

widespread in general population whereas the main sources of EDCs in aquatic environment are due to scattered dwellings, municipal treatment plants and waters from agricultural fields (Table 17.2). Literature published in 2005 reported consumer's intake even for long-term exposure is always lower than acceptable daily intakes (ADI) [38] whereas 26.7% samples showed a significant upward trend in the later years. Highest concentration of EDCs was determined from the tissues of humans or animals present at the top of food chain. Several studies are available to present the difference between ADI and EDI [37].

Passive samplers also proved the presence of pesticides in streams. Denmark government in 1995 published a report to explain disorder of the reproductive system caused by the pesticides influence. In 2002, work of national strategy about EDCs was presented and in 2008 a booklet containing information on EDCs effects especially on pregnant women as well as parents of small children was published by Danish Government. Danish EPA [2012a] published an information booklet with title "Expecting a baby? Advice about chemicals and pregnancy" after survey between July 2011 and March 2013 [39]. It has been determined that ≤0.1% pesticide of total pesticides for weed reached to its target site while rest is lost via photo degradation, spray drift, etc., thereby increasing the crop protection cost as well as severe environmental consequences. Although pesticides are indispensable for crop protection or to fulfill energy needs yet techniques to improve the efficacy, to reduce residue concentration in food chain or in environment are still in infancy. It can be concluded that current agricultural pesticide uses, objectives and their related policies failed in many aspects beyond their sustainable practice.

Pesticides and Human Health

Large scale causalities in the start of the twentieth century due to exposure with heavy concentration of pesticides resulted in general public awareness. More than 4000 cases of porphyria due to HCB ingestion was reported in Eastern Turkey from 1956 to 1961 [40]. Between 1968 and 1979, strong positive relation was developed between "Yusho" (oil disease) and contaminated cooking oil. In 1962 and 197, use of well-known herbicide, orange agent including 2,3,7,8-tetrachlorobenzo-p-dioxin (TCDD) is correlated with chronic lymphocytic leukemia, chloracne, Hodgkin's disease [41]. It has also investigated (Fig. 17.4) that heart diseases, hypertension, depression, respiratory disorders, skin disorders, non-insulin dependent diabetes mellitus (NIDDM, type 2 diabetes) are strongly associated with pesticide exposure [42].

Likewise, mass poisoning incidences indicated that pesticides are toxic at high levels. Serious health issues like birth defects, diseases, and deaths are associated with exposure of humans or animals with pesticides at high levels. The specific health issues can be allergies, cancer, immunological disorders, and reproductive health concerns. A causal relationship between chronic effects of low exposure of pesticides as compared to acute toxicities with high concentration has been developed which initially not possible. According to WHO reports

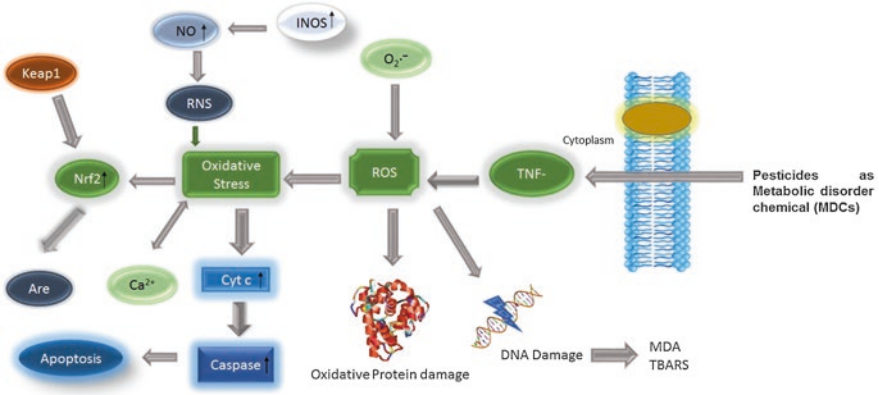


Fig. 17.7 Role of pesticides as MDCs

[WHO, 2012] different types of cancer, i.e., prostate, breast, testicular cancer, etc., [43] increased risks of testicular germ-cell tumors [44], female reproductive dysfunction [45], decreased semen quality, hypospadias, and behavioral or cognitive deficits are associated with chronic exposure of lower concentration of pesticide [46]. However, othet behavioral and cognitive deficits are related with severe deficiencies of thyroid hormone which are strongly associated with bisphenol A, phthalates, PBDEs, perfluorinated chemicals, and PCBs [47]. International Agency for cancer research investigated that pesticides like lindane (g-hexachlorohexane, HCH), OCs, and DDT are potent carcinogens [48].

Pesticides as EDCs

Organochlorine pesticides including DDT, lindane, chlordane, dieldrin, etc., influencing the nervous system, reproductive and immune system are actually endocrine-disrupting chemicals (EDCs) [49]. Very strong evidence regarding relationship between metabolic disorders and pesticide is present. EDCs (Fig. 17.5) are associated with obesogens, higher body weight, NIDDM, metabolic syndromes, hypertension, atherosclerosis, increased TGs [50]. Approximately 31% fungicides, 46% herbicides, and 21% herbicides are identified as EDCs [51]. Ten EDCs like maneb, zineb, penta chloronitrobenzene, prodiamine, amitrole, etc., are strong inhibitors of thyroid hormone [52].

Metabolism of Pesticides

Enzymatic catalysis converts pesticides into hydrophilic intermediates via phase I and phase II [53, 54]. Enzymes in phase I are usually the members of cytochrome P450 family, e.g., heme-thiolate proteins are the major enzymes belong to cytochrome

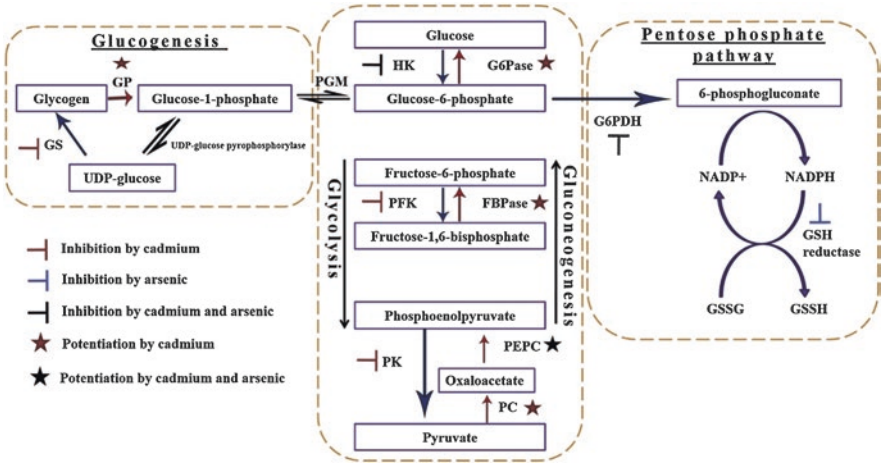


Fig. 17.8 Role of arsenic and cadmium on the activity of various enzymes involved in carbohydrate metabolism [129]

P450 superfamily (CYPs) involved in phase I metabolism. Other enzymes like flavin monooxygenases, amine oxidases, xanthine oxidases, peroxidase cause the oxidation of different functional groups whereas hydrolytic reactions are carried out by epoxide hydrolase and carboxylases (Fig. 17.6).

After phase I, the products do not eradicate quickly, but have to go towards other successive reactions in which substrate like *glucuronic acid, sulfuric acid, acetic acid,* or an *amino acid* joins with the exposed functional group to synthesize highly polar molecules that makes their excretion very easy [55]. Enzymes are classified into phase I oxidative, phase II conjugative, or phase III transporters on the basis of pesticide degradation mechanism in the human body. Enzymes of phase I produce such functional groups that may provide exposed site for conjugation by *UDP-glucuronosyltransferases (UGT), sulfotransferases (SULT), glutathione S-transferase (GST), and N-acetyltransferase (NAT)* of phase II enzymes. Enzymatic metabolism of pesticides is an indispensable process for transformation of lipophilic foreign compound into water-soluble products that can be easily excreted in urine. Expression of phase III transporters such as *P-glycoprotein (Pgp)*, *multidrug resistance associated proteins (MRPs)*, and *organic anion transporting polypeptide 2 (OATP2)* can be visualized in the liver, intestine, kidney, and brain where they play a crucial role in pesticide distribution, absorption, and excretion.

In addition to phase I and phase II reactions, induction, inhibition, or pretreatment with many inducers along with various inhibitors exhibit the change in the expression of phase III transporters, leading to final elimination of pesticides from the body. Exposure of pesticides to phase I, phase II, and phase III inducers may cause the activation of cellular stress that boost the gene expression, which facilitates the removal of pesticides [56].

Role of Pesticides as EDC in Metabolic Disorders (MDs)

Various pesticides like DDT, DDE, HTPE have ability to significantly amend the gene expression, alter the secretion of hormones, volume or number of adipocytes, body weights and function of adipose tissues, location of cells, signaling pathways after exposure [57]. Altered genes lead to improper balance between different cell types, organ structure, hormonal signaling, variation in cell number that increases the susceptibly to dysfunctions or diseases throughout the life (Fig. 17.7). Growth factors and hormones are chiefly responsible for the developmental process; therefore, developing organisms are extremely sensitive to agitations created by these pesticides [58]. Most pronounced adverse effects of these pesticides are seen in development with far below levels of pesticides than in adulthood. The sensitivity in development stage is due to the absence of protective mechanisms, i.e., fully functional immune system, detoxify enzymes, blood–brain barriers in newborns [59]. Furthermore, high metabolic rates in development stage may also aggravate the process of toxicity [60]. Another important reason for sensitivity in developmental stages for pesticides is the epigenetic signaling which provides the biochemical basis for the adverse effects of pesticides during maturation [61]. Effect of pesticides on epigenetic signaling, e.g., histone markers, DNA methylation, chromatin remolding, etc., may alter the tissue programming causing obesity [62]. As gene expression is altered due to growth factors, irregular/untimed expression of genes but epigenetics causes the permanent change in gene expression [60]. Strong evidences are present to correlate many chronic diseases including NIDDM, MetS, and obesity with epigenetic amendments under the influence of environmental factors, i.e., chemicals, stress, nutrition, drugs, etc. [63].

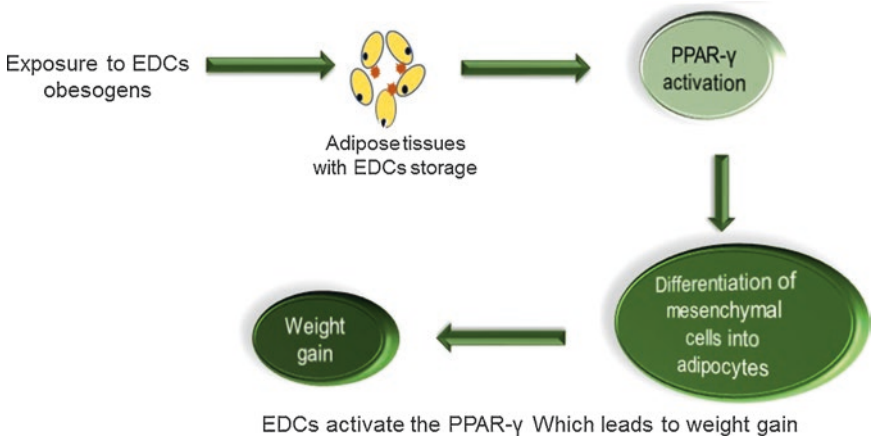


Fig. 17.9 Effect of pesticide on lipids

Effect on Carbohydrate Hemostasis

Pesticides as EDCs exert various negative effects on glucose hemostasis by targeting β-cell physiology. Exposure of pesticides like TCDD and dioxin decrease pancreatic glucose uptake, thus impairing insulin secretion that leads to depletion of cellular insulin thereby rendering β-cells physiology [64]. Many incidences of NIDDM and insulin resistance in Vietnam War after exposure of TCDD have been reported [43]. Another pesticide, TBT by inhibiting glucose proliferation, causing β-cells apoptosis exerts negative effects on glucose hemostasis [65]. Cadmium (Cd) and arsenic (As) from rice as a result of anthropogenic activities alter carbohydrate metabolism causing diabetes mellitus [66]. These contaminants of inorganic fertilizers inactivate various enzymes involved in hexose monophosphate pathway (HMP), gluconeogenesis, glycolysis, and glycogenesis by altering their 3D structure (Fig. 17.8). BPA in pregnant women resulted in body weight gain, glucose proliferation, impaired β-cells as well as insulin instability [67].

Effect on Insulin Resistance

Insulin production or secretion is characterized by feedback mechanism to stabilize the glucose level in plasma. *β-cell* provides great assistance to stabilize the glucose homeostasis during low insulin level in individuals to avoid diabetes type-II [68]. The disease only grows when the bulk for manufacturing sufficient insulin to respond this insulin-resistant state is reduced [69]. Insulin resistance mediated by *β-cell* dysfunctions induces T2D. Along with genetic causes, living lifestyle also provides a major role in insulin resistance. It is also suggested that several EDCs also have provided important role in developing metabolic disorders. Many EDCs such as several pesticides cause the dysfunction of *β-cell* leading to insulin resistance in mouse models. These EDCs accumulate in human blood and act as estrogens by binding with specific cellular receptors to block or disturb the hormonal activity by creating insulin resistance. In vivo exposure of EDCs to pregnant mice disturbs the glucose metabolism followed by insulin resistance that leads to hormonal dysfunction in offspring [70].

Particularly, not each person with obesity carries insulin resistance, a *phenotype* generally named as a healthy metabolic obese. On the other hand, individuals with usual weight that have severe metabolic disorders followed by insulin resistance and type 2 diabetes, have a *phenotype* stated to as metabolically obese with normal body weight [71]. There are common numbers of these two groups: 31.7% of US obese individuals are metabolically healthy and 23.5% of normal-weight individuals are metabolically abnormal [72]. Literature reported that EDCs interact with insulin receptor substrate (IRS), Akt, PI 3-kinase, PKC, or by other associated mechanisms

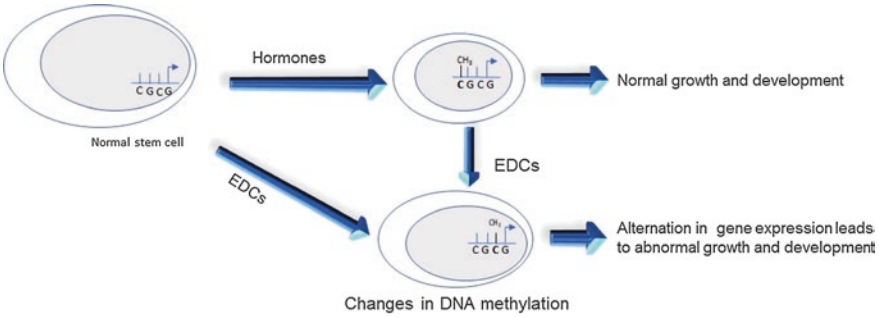


Fig. 17.10 Effect of pesticide on DNA

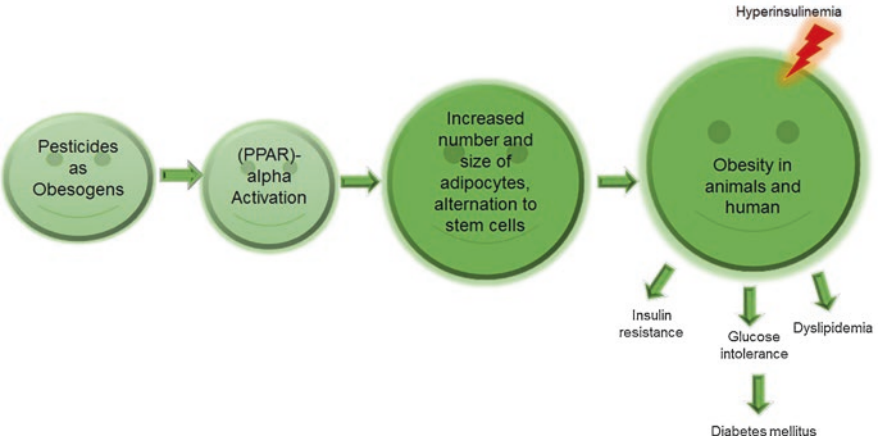


Fig. 17.11 Effect of pesticide as MDCs on obesity

[73]. That is why EDCs accumulating in plasma cause insulin resistance and consider as risk factor to cause metabolic disorders leading to type 2 diabetes [74].

Effect on Proteins

Protein damage caused by ROS in blood, tissues, and cells can be indicated by measuring the protein carbonyls (PCs) that are biomarkers of protein oxidation [75]. The effect of MDCs on protein peroxidation has rarely studied. It has been studied that commercial chemicals containing FIP has lethal effect on carp tissues when applied under rice field conditions. It increases the number of protein carbonyls just after 30–90 days with small dose (0–0.65 mg/L) under rice field conditions [73].

Effect on Lipid Metabolism

Several evidences are available to indicate that exposure of MDCs during developing stage can induce severe metabolic disorders (Fig. 17.9) such as obesity, insulin resistance, hormonal imbalance, and hyperlipidemia [75]. Adipogenesis regulating genes such as *PPARϒ* or some other related genes are main targets for EDCs. During the developing stage, differentiation of mesenchymal stem cells into adipocytes is regulated by *PPARϒ*. *In vitro* study has indicated that when cell lines of mouse embryo exposed to tributyltin, it caused the decrease in *DNA methylation* in promoter region by increasing the differentiation into adipocytes [76]. Such adipogenesis was also observed in mesenchymal stem cells of human when exposed to *dibutyltin* (DBT), a metabolite of tributyltin. More precisely, the mesenchymal cells of human are more receptive to the treatment than *MSC* mouse, with *C/EBPα* and *PPARγ2* that regulate each other with a positive feedback loop and act as significant indicators for adipose differentiation. Over expression of fat-specific protein-27 (FSP27), (FSP4), and LPL were also seen in these cells leading to fatty liver diseases [77]. When sucrose rich fat diet was given to Sprague-Dawley rats then non-phenolic co-administration *(NP)* increased the food and water intake in mouse along with hepatic echogenicity with changes in many plasmatic aminotransferases. The hepatic echogenicity causes elasticity problems in central vein, inflammatory cell infiltration, and up-regulation of genes inducing lipogenesis such as *srebp-1C, fas, and ucp2* [78].

Exposure of triclosan (TCS) to human mesenchymal cells can cause lipid accumulation by decreasing the expression of adipocyte protein 2 (*ap2*), *lpl*, and adiponectin (adipoq) gene [79]. Oral exposure of *DEHP* to rats with dose amount of 0.05,

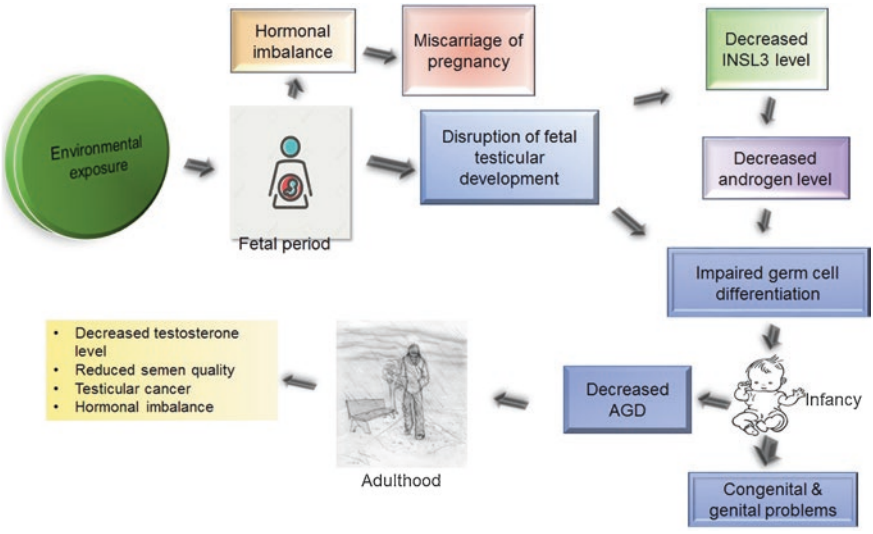


Fig. 17.12 Effect of pesticides on reproduction system

5, 500 mg/kg also causes hepatic steatosis, along with inflammation, *lipid peroxidation,* and damage to the liver and hepatic cells [80]. *DEHP* also induce lipid accumulation in hepatocytes by activating the expression of *SREBP-1c* and *PPARα*-signaling pathway [81].

BPA also have adverse effect on signaling pathways of lipid metabolism. BPA mostly exists in aquatic environment creating reproductive toxicity. BPA increases the triglyceride contents in fish by increasing the lipogenesis along with processing of beta-cells oxidation. Further research is needed to properly understand the adverse effect of bisphenol on the liver metabolism [46].

Damage to Lipids

Oxidative stress created by reactive oxygen species also cause damage to lipids of the cell membrane causing lipid peroxidation that can be measured by noticing the changes in *malondialdehyde (MDA)* and thiobarbituric acid reacting substances *(TBARS)* as being the important individual aldehyde resulting from lipid peroxidation [82]. It has been noticed that continuous exposure of EDCs in vivo models also increases in lipid peroxidation when Fipronil with dose amount (2.5, 5, and 10 mg/kg b.w.) for 28 days given to male Wister rats causing various changes in different organs with increased level of *MDA* [83]. However, in vivo and in vitro dose dependent FIP toxicity creates the oxidative stress that lead to lipid peroxidation and lipid damage in nerve cells [84].

Effect on DNA

Oxidative stress created by reactive oxygen species (ROS) also damage DNA which can be measured by cytokinesis-*block micronucleus* (*CBMN*) assay, *alkaline comet assay,* and by *gel electrophoresis* [85]. It has been investigated that continuous exposure of MDCs *in vivo* animal models also generates ROS that interfere with cell cycle by arresting G2 and M phase (Fig. 17.10). It is the key process for the progression of cell cycle aided by cyclin-dependent kinases leading to decrease in −OH activity and GSH level resulting to DNA damage [86].

Effect on Obesity

Obesity has become a global issue both in developing and under-developing countries in the last few decades [87]. That is why global prevalence of obese people is higher than those who are under-weight [88]. A study has proved that dramatic increase of obesity is due to higher rate of T2D in young individuals, which has

increased the obesity rates followed by intake of high energy meals and deficiency of physical activities. On the other hand, at population level genomic causes are insufficient to clarify the reasons for arising obesity. Epidemiological studies in the last 40 years suggested that chemical changes in environment have played a major role in arising obesity through interfering with major pathways (Fig. 17.11) such as lipid metabolism, energy homeostasis, and adipogenesis [89]. In utero exposure to EDCs has provided the correlations between obesity and environmental obesogens [90].

Grun et al. [91] have also investigated that continuous exposure of MDCs to *in vivo* animal models during embryonic developments cause the adipogenesis. Newborns also showed that exposure of diethylstilbestrol may increase the risk of miscarriage in pregnant women followed by initial loss of body weight in infant. It leads to sudden gain of body weight at puberty, finally causing increased body weight [92]. This study provides the evidences that pesticides as MDCs act on specific targeted pathway to boost up obesity [93].

Influence on Reproductive and Developmental Processes

Pesticides as EDCs damage many physiological reaction of reproductive system which can be manifested *in vivo* or *in vitro* with ovarian and testicular abnormalities [92]. These pesticides increase the rate of breast/prostate cancer, increase testicular occurrence, reduce quality and number of sperms [94]. Effect of these environmental pollutants as sexual defects can also be visualized in wildlife species [95]. These environmental recalcitrants (Fig. 17.12) are also responsible for testicular dysgenesis syndrome (TDS) which includes low sperm count, testicular carcinoma, poor quality of sperms in males whereas diethylstilbestrol (DES) in female reproductive systems [96]. Organochlorine pesticides like chlorpyrifos and methoxychlor alter the biosynthetic pathway of gonadotropin hormones in GT1–7 cells of hypothalamus cells [97]. A study on effect of polychlorinated biphenyl (PCBs) in baby girls reported that PCBs damage the reproductive system in the developmental stages [98]. Reproductive malfunctioning is also observed in the persons working with bisphenol A. Bisphenol A has a property to leach out from plastic utensils, so infants are also at higher danger of ED problems [48]. In females, exposure of BPA is one cause of miscarriage [99]. Miscarriage in experimental animals due to aneuploidy with BPA exposure is also reported [100]. In short, whole hormone release system of humans is a prone target of these recalcitrants.

Effects on Sexual Dimorphism

Many pesticides such as dieldrin being EDCs have ability to interfere with sex limited effects. Data regarding sex is very limited because most of the experiments were performed on males. It is admitted fact that deposition of subcutaneous fats as

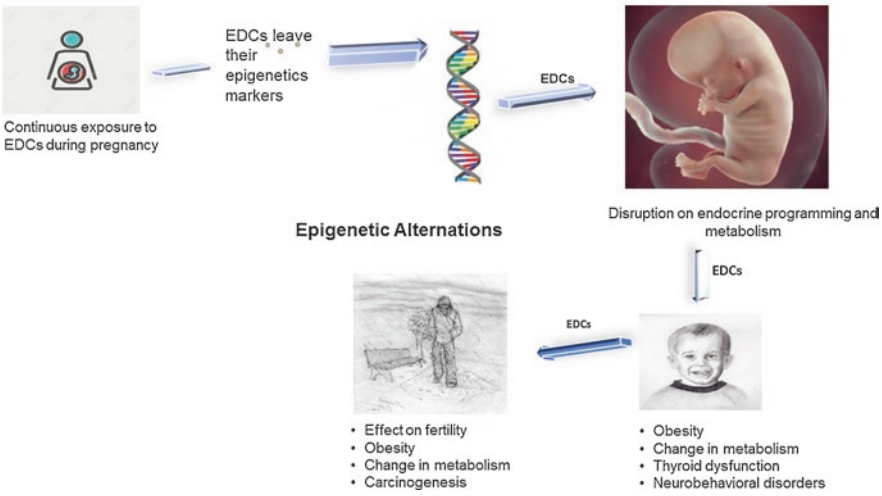


Fig. 17.13 Influence of pesticide on epigenetics

well as endocrine function of adipocytes in females dramatically differs from males, e.g., females have high concentration of adiponectin and leptin [101]. Literature reported that type, dose, time, and metabolic challenge of tested MDCs could feminize or masculinize the energy balancing traits. A significant change in sex dependent body weight has been reported in the experimental animals with exposure of very small concentration of DES or BPA in both pre-natal or post-natal stages. Both, DES and BPA increase the body weight of female rodents without affecting the male rodents [102]. It has further reported that BPA hyper masculinized both male and female mice. Mediobasal hypothalamus (MBH) and pre-optic area (POA) are robustly affected regions of the brain. These results indicated that the brain is the most studied and very sensitive organ for BPA actions [101].

In short, MDCs exposure interferes with normal sexual distinctions of the brain that may reverse or eliminate, diminish or widen the behavioral differences. These behavioral differences may alter metabolic processes. Sexually dimorphic regions of the brain are hypothalamus, cerebral cortex, and hippocampus and these regions are very sensitive to the both pre-natal and post-natal exposure of MDCs. The effects of these MDCs can be observed before the development of gonadal hormones during puberty. Thence, the outcomes of limited research incited the scientists for detail working to determine the sex differences with the exposure of MDCs.

Effects on Energy Homeostasis

In addition to the effects of pesticide exposures on production and action of insulin, these pesticides as MDCs also influenced intermediary metabolic pathways, e.g., TCDD in 3T3-F44a cell lines reduced the lipoprotein lipase expression via

Table 17.3 Different mechanisms of pesticides ROS generation

S. no.	Pesticide	Pathway to generate oxidative stress	disorders	Ref.
1	Pyrethrins	↑Oxidative stress in cerebral and hepatic tissues, ↑TBARS conjugated dienes. ↓ level of total GSH	Neurological diseases	[177]
2	Organophosphates	Chlorpyrifos, to a lesser extent chlorpyrifos oxon, ↑ROS, lipid peroxidation	Neurotoxicity	[178]
3	Organo-carbamate	↓GSH content, ↔ GSSG content, ↓GSH/GSSG ratio, and the induction of glutathione reductase and glutathione peroxidase activities	Erythrocytes damage	[179]
4	Organochlorines	↑Oxidative damage, altered nigrostriatal DA homeostasis, ↑ vulnerability to neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)	Parkinson's disease, apoptosis in human blood	[148]
5	Fungicides	↓Mitochondrial respiration complex III, ↓the natural electron transport, ATP depletion, depolarization of the mitochondrial membrane, ↑ cytosolic calcium level, cell death	Parkinson's disease development, mitochondrial dysfunction	[180]
6	Herbicides	↑Oxidative stress level in the cells → cyclic oxidation/reduction process	‡Lungs, mitochondrial dysfunction, pulmonary fibrosis, hypoxemia, death	[181]
7	Insecticides., Fipronil	¦Human α_1, $\alpha_1\beta$, α_2, and α_3 glycine receptor subtypes. It may induce oxidative stress leading to ROS generation	‡To cellular macromolecules, such as lipids, DNA, and proteins	[117]
8	Dioxins., TTCD	Interaction with AhR and subsequent ↑ cytochrome P450 1A and 1B, ʒ ROS	Immunotoxicity, ‡ liver, wasting syndrome, and cancer	[182]
9	Alkylphenols	Nonylphenol elicits depletion of antioxidant defense system and induces oxidative stress	Reproductive and developmental disorders	[183]
10	Phthalates	Due to mitochondrial dysfunction, ATP production and oxygen consumption are impaired ROS production	Insulin resistance, liver damage, allergic symptoms, infertility and effects on pulmonary function	[75]
11	Polybrominated diphenyl ethers	BDE-47 can induce oxidative stress by ROS formation, causing oxidative ‡	Neurobehavioral‡, immun-otoxicity, reproductive, developmental effects, possibly cancer	[116]

(continued)

Table 17.3 (continued)

S. no.	Pesticide	Pathway to generate oxidative stress	disorders	Ref.
12	Parabens	Butyl paraben stimulates intracellular ROS production leading to apoptosis	Neurological, reproductive diseases, mitochondrial dysfunction	[184]
13	Heavy metals	Copper promote ROS formation in cells	Neurodegenerative disorders, autism, and Alzheimer's disease	[185]

hypertriglyceridemia [103]. Exposure of PBDE inhibited the adipocyte glucose oxidation whereas enhanced the isoproterenol induced lipolysis thereby increasing circulatory FFAs, a substrate for hepatic TG synthesis [104]. Prenatal exposure of 4-nonylphenol may cause lipid abnormalities via high serum cholesterol levels [105]. Sub-chronic exposure of malathion induced hyperglycemia via accelerating glycogenolysis and gluconeogenesis [106].

Impaired glucose and lactate handing in both liver and muscles with chronic intake of DEHP has been reported resulting in variation of glycolytic intermediates [107]. Exposure of BPA in experimental model animals during lactation and utero period proved reduction in hepatic glycogen contents. Reduction in hepatic glycogen contents is due to hypo expression of hepatic glucokinase because promoters of this enzymes were hyper methylated after the exposure of BPA [108]. BPA exposure in multigenerational animal models also supported that glucose intolerance as well as insulin resistance in F0 and F2 generations was associated with hypo expression of hepatic glucokinase by hyper methylation of its promoter gene [109]. These evidences suggest that disruption in hepatic glucose management is a common mode which is promoted by all MDCs in metabolic dysfunctions

Effects on Epigenetics

Epigenetic markers are specific factors around the DNA that play a major role for the determination of functional output about the information, stored in the organism's genome Literature reported that exposure of xenobiotics causes the obesity which can be transmitted to next generations through these epigenetic markers [110]. After the initial exposure, a generation will be called transgenerational until a trait remains persistence in at least two generations [111]. Generally, there are clear evidences that MDCs causing obesity through directly binding with NRs receptors recruiting methyl and acetyltransferase which may lead to changes in epigenetic markers that regulate the genetic expression (Fig. 17.13). So, it reveals that MDCs have ability to change the chromatic state of DNA or histone methyltransferases [112]. Adipogenesis regulating genes such as *PPARγ* or some other related genes are main targets for obesogens. During the developing stage, differentiation

of mesenchymal stem cells into adipocytes is regulated by *PPARɤ*. In vitro study has shown that when cell lines of mouse embryo exposed to tributyltin, it caused the decrease in DNA *methylation* in promoter region by increasing the differentiation into adipocytes [113]. A decreased methylation of 3*CpG* sites causes the alternation in expression of PPARɤ*2* [113]. In vivo study also has shown the lipid accumulation in adipocytes will increase the expression of adipogenesis markers PPARɤ *and* FABP4, when adipose-derived stem cells (ADSCs) obtained from white adipose tissue of *C57BL/6J* mice were exposed to tributyltin [114]. These results showed that adult parents, (f1) generation with increased adipocyte activity will born F2 offspring having the same size of adipocytes having high expression of PPARɤ, COX2, and CEBP*α* [115]. Same alternation was also observed in F3 generation with many other pathologies. This study also revealed that male obesity is transmitted by female germline and vice versa [115].

Effect on Oxidative Stress

ROS are known to have destructive nature that have lethal pathophysiological effects on organs since the last 30 years. Free radicals have atoms with one or more unpaired electrons that induced oxidative stress resulting in lipid peroxidation and also effect body's antioxidant defense system (Table 17.3). It is clear evidence that oxidative stress can cause various diseases like Alzheimer's Disease, Parkinson's Disease, cataracts, atherosclerosis, neoplastic diseases, diabetes, chronic inflammatory [116].

Pesticides as MDCs are toxic chemicals that target biological system due to their adverse toxic potential. Oxidative stress produced by pesticide remained a toxicological research topic for the last many decades. A number of research projects have been conducted to determine the toxic effect of these deleterious agents. It is necessary to understand the production of free radicals before studying the adverse effects of oxidative stress [175]. Numerous biological responses are initiated by oxidative stress created by these pesticides. *In vivo* and *in vitro* study reported the role of selected pesticides in creating oxidative stress. Oxidative stress caused by ROS also induced death receptor pathways such as tumor necrosis factor receptor (TNFR) followed by activation of tumor necrosis factor alpha (TNF-α). After the ligation process that leads to activation of *caspase-8* which then cleaves effector caspase-3. The high number of *TNF-α* leads to productions of reactive oxygen species as seen in rats when exposed with *permethrin* [76]. *Nurr1* which is a transcription factor of family NR4A proteins plays a significant role in the metabolism of dopaminergic neurons by inhibiting activity of the *transcription factor NF-κB* in the brain tissue [60]. ROS creates oxidative stress that causes lipid peroxidation which then effect the activity of *Nurr1* followed by the induction of *NF-κB*. At the same time exposure of permethrin increased the expression of *proinflammatory NF-κB transcription factor* by accumulating *Nurr1* gene in experimental animal models [117].

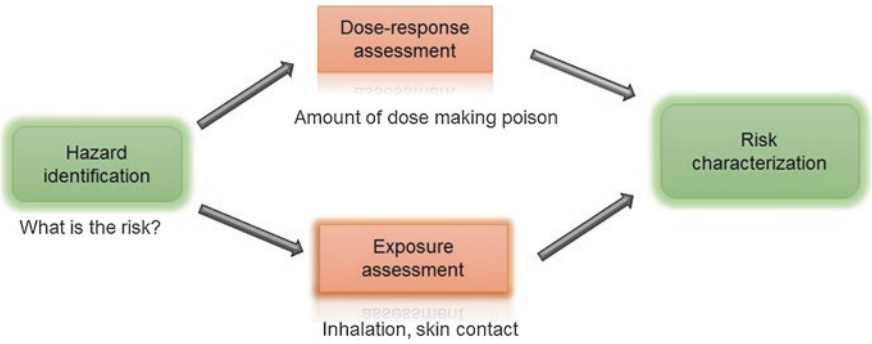


Fig. 17.14 Understanding the risk factors of pesticides

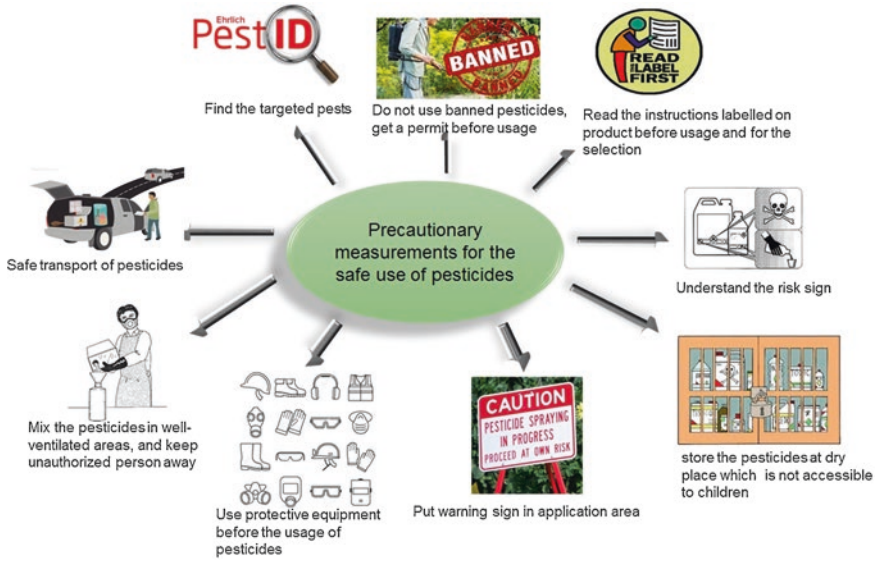


Fig. 17.15 Safety precautions during handling of pesticides

Pesticides such as paraquat mostly used in agricultural areas interferes with electron transport chain of photosystem thereby inducing mitochondrial toxicity. In cytosolic compartments and plasma membrane, paraquat acts as redox cycling compound that is initiated by *NADPH* oxidase, nitric oxide synthase, and *NADPH*-cytochrome P450 reductase. The reduction of paraquat into $PQ^{\cdot}$ + is catalyzed by NADPH-cytochrome P450 reductase that leads to generation of $O_2^{\cdot -}$ that takes part in oxidation and reduction cycle. All NADPH-dependent enzymes that take part in metabolism of paraquat also affect glutathione disulfide recycling to GSH. Just like to permethrin, paraquat also causes changes in expression of *Bcl-2 and Bax* by releasing cytochrome c into cytosol [118].

Effect on Alterations in Antioxidant Status

GST, SOD, GR, GPx, and *CAT* are some enzymatic antioxidant defense systems that protect the cell from damage caused by reactive active species such as (O^{-2}), (*–OH*), (H_2O_2) (1) (2). GSH is an intracellular molecule that mediates the activity of *GST, GR, GPx* by acting as substrate or co-substrate and protects the cell from damage [119]. *GR* as a component of G6PDH plays a key role in antioxidant system by reducing NADPH [120].

In vivo and *in vitro* continuous exposure of MDCs in animal models also generates reactive oxygen species by changing antioxidant status of the organs or tissues altering the expression of antioxidant pathways in the liver such as *Gsta2, Gstm1, Gstm2, Gsta4, Gsta5, Gstp1, and Gstt2 mRNA* [121]. Different factors like dose and time of MDCs exposure are studied during *in vivo* and *in vitro* trial; however, various factors are still unclear which need further research to understand the effect of MDCs on antioxidant status of the cell.

Effect on Apoptosis and Cell Cycle

Apoptosis is triggered by oxidative stress created by reactive oxygen species (ROS) [122]. Apoptosis is a programmed cell death followed by the denaturation of cell membrane, production of apoptotic bodies, and fragmentation of nuclear membrane [123]. It has been investigated from continuous exposure of these pesticides to animal models that generates reactive oxygen species which interfere with cell cycle by arresting G2 and M phase. It is the key process for the progression of cell cycle aided by cyclin-dependent kinases [124].

Intervention of Safety Measures from Pest Control Operation

Preventive measure costs half (2.48 times lower) than medical treatments because half of persons working in the fields did not use any preventive measures [125]. These findings open a new horizon on the topic of safety measures among directly exposed persons in developing countries [126]. Economic empowerment, implementing training programs, extensive awareness schemes, formal educations should be important to lessen health risks as well as health costs among directly exposed persons [127]. Specific safety measurement must be followed during the storage, transport, and usage of these pesticides. Safe use of these pesticides depends on many factors such as selection of product, usage of product according to safety instruction written on packing, and legal uses of product.

Pesticides Risk Understanding

Some pesticides are dangerous while others are safe but the term "safe" and dangerous have some confusions. Any types of chemical that may also include pesticides are hazard for both humans as well as environment. So, proper understanding of risk regarding pesticides (Fig. 17.14) will lower the deleterious effects [26]. The negative effects of pesticides depend on two factors (1) exposure (2) toxicity. Exposure means how much amount we have taken into our body whereas how poisonous it is for environment and humans both. Any pesticide even having low toxicity but with high exposure can be hazardous to human. Risk will be doubled with elevation of pesticide. Pesticides are mixture of more than one chemical and every chemical has its own level of toxicity. It is the reason, we must follow the "signal words" written on packing of pesticide because these represent the toxicity levels before their use. The word "Caution" means low in toxicity, the term "Warning" indicates medium toxicity level while "Danger" represents the higher toxicity level [128].

Precautionary Measures

Consider these precautions while using and handling pesticides (Fig. 17.15):

- Target pest must be identified.
- Pesticides must be labeled according to the instructions of WHO. The precautions must be written in English and local language for better understanding of the users.
- Pesticides must be kept in its original container and stored in such places that are not accessible to children or pets.
- Follow safety measure and wear protective clothing such as long sleeve shirts, long pants, protective rubber gloves, and any other protective equipment according to labeled instructions while using.
- Mix the pesticides in ventilated area and make sure that children, pets, or any other person are not present in that area.
- Remove personal items such as toys, furniture, bags, and clothing's before use.
- Spray workers must wear long sleeves with mask, protective hat, and long shoes.
- Keep these pesticides in dry places.
- Safely disposed these pesticides into dug hole in the ground. It should not dispose in such areas where fresh water is running.
- After using pesticides, wash your hands. Most of the pesticides required permission from agricultural officer before the use of pesticides. Remove the workers from agricultural land during application period and put warning signs and also mention safe re-entry date.

Conclusion

It is necessary to answer with scientifically proven facts to problems of pollution. National agriculture policies should be formulated that encourage and insist farmers to use ecofriendly alternative strategies to control pests such as organic farming. Agriculture policies like (1) assessment of pesticide's role in environmental pollution (2) development of pest resistant crops through genetic engineering or biotechnology (3) new integrated approaches to control pests are required to limit the uses of pesticides. One another alternative of pesticide is to use natural pesticides (limonene, pyrethrum), inorganic materials (diatomaceous earth, boric acid), biological agents (parasites, microorganisms). These strategies are assumed to be noxious for both humans as well as environments.

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Chapter 18
Role of Perfluoroalkyl Substances as EDCs in Metabolic Disorders

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Abstract Perfluoroalkyl substances (PFASs) belong to a class of compound that hold at least one fluorine atom, are being used in several consumer and industrial goods because of their special chemical properties, such as the capability to repel oil as well as water. It is of great concern that these dangerous chemical compounds are now present in the whole global environment. Humans are exposed to the PFASs by drinking polluted water, ingestion of contaminated seafood, inhalation of infected indoor air, and making contact with contaminated media of any kind. A complex state is characterized by raised level of blood glucose, abdominal obesity, abnormal lipid amount, hypertension, and insulin resistance. It is one of the major causes for stroke, cardiovascular disease, chronic disease of kidney, T2D, and cancers. With increasing obesity, the incidence of metabolic syndrome is rising. Rising evidences suggested that raised body mass index (BMI) is not only associated with calories rich diet and sedentary lifestyle, but also coupled with extensive environmental exposure to obesogens like perfluoroalkyl substances (PFASs). A variety of animals studies have suggested that exposure to PFASs can impair lipids and carbohydrates homeostasis, change composition of fatty acid, and alter adipocyte differentiation,

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although results have been conflicting. A number of epidemiological investigations reported links between high level of perfluorooctanesulfonic acid or perfluorooctanoic acid (*PFOA*) in maternal serum and enhanced BMI of offspring, possibility of being obese, and low level of serum leptin levels in kids or adults. Particularly, females are more pronounced to these effects. PFASs possess properties helping in long-range transport by allowing enough residence time in the atmosphere and simultaneously they are so reactive that they are easily convertible into carboxylic acids and other compounds such as fluorotelomer species by undergoing oxidative reactions.

Keywords Perfluoroalkyl substances · Adipocyte differentiation · Obesogens · Fluorotelomer species

Introduction

"Fluorinated substances" is a common term that defines a class of organic and inorganic chemicals that holds at least one fluorine (F) atom, with immensely varied chemical, physical, and biological effects [1]. Synonyms include "fluorochemicals" and "fluorinated chemicals." A subclass of fluorinated chemicals is the extremely fluorinated aliphatic chemicals that contain one or more C atoms on which all the H substituents have been exchanged by F atoms, in a way that they possess the C_nF_{2n+1}– functional group. Therefore, these compounds are called "perfluoroalkyl and polyfluoroalkyl substances" and represented by the abbreviation PFASs. PFASs and polymers made with the aid of PFASs and surfactants have been extensively utilized in several commercial and industrial applications since 1950 [2].

Polyfluoroalkyl substances can also be defined as those aliphatic chemicals for which all hydrogen atoms attached to at least one carbon atom (but not all) and these hydrogen atoms have been replaced by F atoms, in such a fashion that they have perfluoroalkyl functional group C_nF_{2n+1}– (for example, $C_8F_{17}CH_2CH_2OH$). Consequently, however the overall chemical conception of "polyfluorination" encircles compounds having "scattered" several F atoms (e.g., in $CH_2FCHFCHFCH_2OH$), likewise "grouped" ones (e.g., $CF_3CF_2CH_2COOH$), polyfluorinated substances having minimally one perfluoroalkyl moiety C_nF_{2n+1}– are considered that they belong to PFAS family, as an extensive range of these chemicals have been detected in the environment, humans, and wildlife due to the increased usage of PFASs and their release in the environment. The universal extent of such kind of pollution was first described in wildlife for perfluorooctane sulfonic acid, $C_8F_{17}SO_3H$ (PFOS) by Giesy and Kannan [3].

Under suitable conditions, polyfluoroalkyl substances have the capacity to be transformed biotically or abiotically into PFASs. Such as polyfluoroalkyl substance $C_nF_{2n+1}SO_2NHCH_2CH_2OH$ can break down to PFASs, i.e. $C_nF_{2n+1}SO_3H$ [4, 5]. This concept was revealed by groups of the scientist who have participated in the European Union PERFORCE project [6] and some other scientists who have

followed them. Soon afterward, many researchers defined it in various other ways and started to use the acronym PFC. Consequently, the acronym PFC meaning is not clear and well described. Furthermore, this choice has been considered inappropriate and unfortunate. In Kyoto Protocol documents acronym PFC has been used officially since 1997 to specify the perfluorocarbons [7].

PFAS Nomenclature

One perfluoroalkyl moiety (C_nF_{2n+1}-) is present in all PFASs at least [8], whereas substances with incomplete hydrogen atom replacement by F atoms are known as polyfluoroalkyl substances. Perfluoroalkyl acids (PFAAs) comprise perfluoroalkyl sulfonic, carboxylic, phosphinic, and phosphonic acids and based on their functional group, they are differentiated. Perfluoroalkyl sulfonic acids (PFSAs) and perfluoroalkyl carboxylic acids (PFCAs) have been the main area of focus for the research with 4–16 carbon atoms (C4–C16). We can define long-chain PFASs as PFCAs with 7 or greater perfluorinated carbons and those PFSAs having six or greater perfluorinated carbons. Presence of fluorinated carbon chain enables these chemicals to have both oleophobic and hydrophobic properties but deprotonation of head group of many PFASs makes them highly stable in solution. High solubility of PFASs in water results into their accumulation in rivers, groundwater and ocean, and pollution of resources of drinking water marine mammals and fishes. Precursors of PFAA, which are referred to as "precursors," are chemical compounds that can be broken down to PFAAs biotically or abiotically [9, 10]. Before disposition in the areas that are far away from the sources of pollution volatile precursors may be conveyed to long distances in the atmosphere [11, 12]. During the analysis of standard PFAA mostly precursors are not measured, which may result in under estimation of exposure to humans as they are degraded to short-chain PFAAs in the human body [13, 14].

Chemistry and Chemical Properties

Perfluorooctanesulfonic acid (PFOS), perfluorooctanoic acid (PFOA) and their derivatives are the most known chemicals among PFASs.

Chemical Properties

- PFOS, PFOA and their salts are soluble in water and may globally spread through seawater currents [15].
- The most commonly used structures are more complex derivatives of these chemical substances, for example, fluorotelomers and sulfonamides.

- Degradation of these complex derivatives results into formation of PFOA, PFOS, or perfluoro alkanoic acids with longer or shorter perfluorinated alkyl chain; the tail of which is made of perfluorinated chemicals and cannot be degraded in the environment and living body [16, 17].
- More complex derivatives of these chemicals are insoluble in lipids and water but volatile to some extent and their transportation can occur by air from temperate to arctic regions over longer distances [18]. The most common source of human exposure to PFCs is the utilization of derivatives of fluorotelomer in firefighting foam [18, 19].

Uses of PFASs

PFAS are used in several consumer and industrial goods because of the especial chemical properties of these chemical compounds, such as the capability to repel oil as well as water. Norwegian market has been introduced with an enormous variety of PFASs through industrial usage (such as through paint and firefighting foams) and in other customer products (e.g., coated paper and textiles). Our current knowledge of correct compositions of PFASs by using perfluorinated chemicals is inadequate. This inappropriate knowledge indicates that accurate measurements about the exact exposure to humans are very difficult, furthermore, the amount of waste present in treated products is also difficult to measure. It is of great concern that these dangerous chemical compounds are now present in the whole global environment [20].

Because of the toxic effects of PFASs, attention has been directed towards their exposure to humans. Fluorotelomer alcohols, perfluoroalkyl sulfonic acids and carboxylic acids were detected in 115 samples taken randomly of different consumer goods including carpets, textiles (outdoor materials), impregnating and cleaning agents, sandwich and baking papers, leather samples, and waxes. PFASs are detected by HPLC-MS/MS, while FTOH are analyzed by GC/CI-MS. A negligible amount of PFCA and PFSA is present in some consumer goods such as sandwiches and baking papers and cleaning agents. Whereas some consumer products contain high level of PFAS such as leather samples (up to about 200 μg/kg PFBA and 120 μg/kg PFBS), ski waxes (up to about 2000 μg/kg PFOA), outdoor textiles (up to 19 $\mu g/m^2$ PFOA), and other baking papers (up to 15 $\mu g/m^2$ PFOA). Furthermore, a few samples like leather and carpet samples and some outdoor materials have excess EU regulatory threshold amount for PFOS (1 $\mu g/m^2$). Products of our daily usage contain a diverse variety of PFASs in different concentrations [21].

Environmental Fate of PFAS

The fate of environmental PFAS describes their transportation, partitioning, and processes of transformation after the release of these chemicals into the environment. During and after the manufacturing and utilization of PFAS-containing goods, the waste containing PFASs is released into the aquatic environment.

Typically precursors of PFASs are transported through the atmosphere due to their semi-volatile to volatile properties and consequently maybe break down to PFCAs and PFSAs [11, 22]. The precursors of PFASs (such as FASAs, FTOH, PAPs, FASEs) undergo through various pathways of transformation in the air or under anaerobic or aerobic conditions in other environmental compartments [10, 22]. Furthermore, other intermediate products of degradation (i.e., FTALs, FTUALs, FTUCAs, FTCAs) produced during both biotransformation and atmospheric transformation are extremely reactive [11, 23] and have revealed toxicity of both kinds, i.e. acute and chronic to the aquatic green algae and invertebrates [24, 25]. The transportation processes of end products of degradation occur principally in the water phase but can also take place through gas-phase, sea spray, and atmospheric particle-bound transport [26–28]. For distant areas, such as Arctic Ocean, PFASs long-range transportation was predicted to be 1–2 times higher in the water phase as compared to atmospheric transport [29, 30]. Nevertheless, still it is under discussion whether the water phase transport or atmospheric transport is the pathway of transportation for ionizable PFASs, Moreover, for volatile, neutral PFASs most dominant pathway of transportation to remote areas is gas-phase transport [31]. Various environmental conditions (e.g., salinity, content of organic carbon, temperature, and atmospheric oxidants concentrations) are responsible for the environmental cycling of PFASs and some of their inherent physicochemical properties. Furthermore, functional groups and PFASs chain lengths also determine their degradation. Short-chain PFASs are more mobile in the aquatic environment and hydrophilic, while long-chain PFASs have more hydrophobicity, therefore, have the ability to bind to particles and show the potential of bioaccumulation [32, 33]. Sediments and oceans are the largest sources of PFASs [30].

Exposure, Bioaccumulation, and Effects in the Aquatic Ecosystem

PFASs possess a high affinity to bind to fatty acid-binding proteins and serum albumin which consequence in a tissue-dependent supply in biota [34]. Such as tissue distribution for PFASs in a variety of species of freshwater fishes from Beijing, China reduced from brain to muscle and blood over the liver. Furthermore, the potential for bioaccumulation for PFASs is different for individual species and organisms based on the physicochemical properties of PFASs, either it has linear or branched chain or functional group and chain length [32, 35]. It has been revealed that the rate of elimination based upon the structure of PFASs, e.g. the rate of elimination of branched isomers is faster than linear ones. Moreover, the elimination and bioaccumulation of PFASs are also based on the gender, species, and status of reproduction. PFASs exist in the environment universally, even in pristine areas, and may also be biomagnified with the food chain [36]. The most dominant PFAS in biota is PFOS (C8 fluorocarbon), and the concentration of PFOS enhances with the food chain, exhibiting its high potential of bioaccumulation. Distinctly, bioaccumulation potential of perfluorooctanoate (PFOA; C7fluorocarbon) is low and is quite

alike among different trophic level species. For example, the highest concentrations of PFOA and in invertebrates [37] are similar in range, whereas in reptiles [38], fish [39], mammals [40, 41] and birds [42, 43] the maximum concentration of PFOS is up to 3 times of magnitude is higher in comparison with PFOA. The lower potential of bioaccumulation of PFOA may be due to the length of the perfluorocarbon chain and difference in the functional group in PFOS compared with PFOA [32]. Due to the phase out of PFOS, in a recent time period, PFSA concentrations showed declining rates in biota in 2002 [44–46]. However, no clear trend has seen in the other PFASs concentrations, for example, long-chain PFCAs are rising in concentration depending on trophic level, the compound, and different geographical location [47].

Therefore it is considered that PFAS is persistent as a whole in the environment, while precursors of PFAS can be degraded to PFSAs and PFCAs [10]. In the aquatic ecosystem continuous introduction of PFAS can consequence in constant exposure of such chemical compounds for those organisms that are present in the depth of discharges. From these observations, it is concluded that aquatic organisms suffering discharges of waste water and other sources of PFAS are more exposed to these hazardous chemicals [48]. Only a few numbers of studies deal with implications of this fact over various generations [49]. Survival of juveniles was assessed by Drottar and Krueger in 2000 (over 48 hands 96 h) released from Daphnia Magna (freshwater Cladocera) that was exposed with PFOS and Mysidopsis Bahia (marine Mysida) in medium contaminated with the same concentration of PFOS as the media adults had been living. After this short time exposure of PFOS shift insensitivity indications were not exhibited by Daphnia and Mysidopsis. Studies were conducted with invertebrates, Japanese medaka (Oryzias latipes) was exposed to either PFOS or PFOA (in the mgL1 range) discharged offspring that showed a high rate of mortality and alterations in the histopathological pattern even after the hatching in controlled medium (PFAS-free) compared with the progeny discharged from control animals. If the exposure was continued with F1 generation the effect was more pronounced [50]. So, it is concluded that if a species exposed to PFOS or PFAS for one generation the effects can be observed on the next generation. If the aquatic ecosystem continuously being exposed with polyfluoroalkyl and perfluoroalkyl substances the next generations will continuously show after effects, studies should be conducted to assess the potential implications over multiple generations particularly for those generation having short generation time, e.g. Daphnia or Chironomus. Experiments should be performed to analyze multiple generations to see whether hazardous effects persist even in PFAS-free media (controlled conditions) by simulating the species migration to nearby unpolluted aquatic media. Overall, hazardous results of PFASs should be evaluated considering a continuous exposure to the environment.

Occurrence and Exposure in Relation to Humans

In the past short-chain, PFAS was found in minor constituents of long-chain PFAS or as a contaminant but in recent times utilization of short-chain PFAS is increasing day by day as an alternative for C8-PFAS. Still, it is largely unclear which source of

PFASs is the biggest one for the human body exposure to these dangerous chemicals whether it is indoor or ambient air inhalation, contaminated food intake, drinking polluted water or direct contact with PFC containing goods [51]. Moreover, workplace exposure to these substances may also contribute. Perhaps it depends upon the exposure circumstances which are more important. Serum samples and matched daily diet studies in Japan revealed that only PFOA and PFOS were noticeable in the diet. 23% of the PFAS in serum was detected in the diet in the megacity Osaka, while in a small rural area 100% PFAS was calculated in diet [52].

Occurrence in Products

In past studies, fluorotelomer alcohols were analyzed in less textile goods for kids than 8:2 FTOH and 10:2 FTOH, usually in fewer concentrations and particularly the amount of 4:2 FTOH was less than detectable limits in all researches. In 2014 Dreyer collected 16 outdoor samples from gloves and jackets, all the samples had PFAS. Out of 16 samples, 14 contained PFOA, 13 had PFHxA, and 10 contained PFBA/PFDA. PFASs concentration for the individual samples was in the range of 0.1 and 11 μg/m, FTAs and FTOHs were found in all investigated samples. Volatile PFAS concentrations were 100 times higher than that of perfluoroalkyl acids. Concentrations of FTOH were highest in most of the samples. It was observed that at room temperature all the outdoor jackets emitted volatile PFAS which indicated that such products are important sources of PFAS, more importantly for indoor atmosphere FTOHs.

Accordingly, the rates of PFAS contents emission were also different for different compounds. 6:2 FTOH showed the highest emission rates (up to 9200 ng 6:2 FTOH/d). 2–16 μg PFHxA/m2 was extracted from mixed textile samples [52]. In kids jackets, 6:2 FTOH was dominant PFAS and it was extracted in amount 19 μg/m^2 [53]. In previous Norwegian research of impregnating agents, the most dominant PFASs were PFBA, 6:2 FTOH, and PFHxA. 4:2 FTOH, PFPS, 6:2 FT (U)CA, PFHxS, and 6:2 FTS were found in less than detection limits. Concentrations of extracted PFAS from 5 impregnation agents are as follows: 6:2FTOH = 535–13.250 μg/L, PFBA = 75–142 μg/L, and PFHxA = 23–25 μg/L [54].

Some PFASs, for example, polyfluoroalkyl phosphate esters (PAPs) are also used in the production of personal care products such as manicure, sun cream, foundation, and lip rouge. PAPs is broken down into PFCAs and these chemicals can be found in commercial products [55].

Human Exposure

Humans are exposed to the PFAS by drinking polluted water, ingestion of contaminated seafood, inhalation of infected indoor air, and making contact with contaminated media of any kind [56]. Because of the attractive oil and water repulsive

properties of PFAS, production of PAFS is being made on a large scale so that it can be used in industrial and consumer products. Buch described the classification and terminologies of the PFAS in 2011 as it belongs to a vast class of the compounds [8]. From point of view of regulations, PFSAs and perfluoroalkyl carboxylic acids (PFCAs) that are long-chain PFASs lie in the area of interest. PFASs are considered environmental pollutants, and therefore some manufacturers from the Western countries have stopped their production or halted production or decided to phase out perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) manufacturing in the 2000s. Still, PFASs are detected in humans and wildlife commonly due to continuous manufacturing as well as less biodegradability and because of the production of some other PFASs compounds [45]. The most important source of human exposure to the PFAS is diet such as eggs, fish, and meat [57]. Another source of human exposure to PFAS is indoor dust [58]. Before birth, human exposure to PFAS occurs because of placental transfer [59]. Due to the high immune-toxicants susceptibility, exposure to prenatal toxicants has been considered of great importance because of the in-utero development of the immune system [60, 61]. Besides early childhood complications, toxicant's exposure to the fetus may cause changes throughout life constantly, which may lead to immune diseases and cancers [62].

Rodent studies have indicated that PFASs also exhibit immunotoxic effects. For example, DeWitt explained how the level of IgM antibodies was suppressed after exposure to the PFASs [63]. Peden-Adams described that antibody production was affected by PFOS [64]. The collective facts on rodent studies suggest that the production of antibody is an important endpoint that is sensitive to PFAS exposure [65]. In recent studies, it has been reported that PFASs exposure causes immunotoxic effects in humans. A connection between increased PFAS concentration in blood and decreased humoral immunity has reported. Furthermore many other studies have not suggested any relationship between infectious and allergic responses and PFAS exposure [66]. Evidence of immune-suppression has reported by Granum in prenatal childhood exposure, for example, inverse relationship between the concentration of four PFAS in maternal serum at delivery time and levels of anti-rubella antibodies in the serum sample of 3 years old kid. During the period of the first 3 years of life, a positive connection was found between the maternal concentration of PFASs and the number of episodes of gastroenteritis and the common cold [67]. It is concluded that early childhood exposure to PFAS causes immune-suppression [68].

International Concerns

In the early 2000s, international concern began regarding potential effects to health-related to PFASs exposure when polar bear blood was detected with PFOS in wildlife, arctic, and other remote regions [48]. Initial data on bioaccumulation of PFOS in marine food chains showed the susceptibility of human exposure to PFASs by seafood [69]. Disease control and prevention of the U.S., i.e. Centers for Disease

Control (CDC) investigated that these hazardous compounds were present nearly in all Americans [70–72]. Between 2000 and 2002, the core universal maker of PFASs willingly stopped producing the basic chemical used in the manufacture of PFOS [73]. Various programs were introduced by the USA to control the usage of plenty of environmental PFASs, Stewardship Program was one of such programs implemented in 2006 to stop the long-chain PFASs production by 2015. Moreover, in 2009 PFOS was included in the Stockholm Convention's record of worldwide restricted Persistent Organic Pollutants (POPs).

In Japan and other western countries, PFOA and PFOS exposure to humans has been decreasing over the last 10 years [74, 75] because of these regulatory steps taking into account the increase in dangerous effects on humans health [76]. Whereas, a rapid increase in the use of some other short-chain chemicals in place of PFOA and PFOS that are very difficult to analyze by the use of standard methods [77]. From animal experiments, it has been suggested that alternative PFASs are equally dangerous [78]. Hence, considerable challenges must be faced by environmental health scientists to understand the importance of adverse exposure routes and their effects on human health.

Role of PFASs in Metabolic Syndrome

Metabolic syndrome (MetS) is a complex state which is characterized by raised level of blood glucose, abdominal obesity, abnormal lipid level, hypertension, and insulin resistance; it is one of the major causes for stroke, cardiovascular diseases, chronic kidney disease, type 2 diabetes mellitus (T2DM), and cancers [79, 80]. With the increased rate of obesity, the incidence of MetS is rising [81]. In the past few years, it has been observed that metabolic diseases have greater associations with hereditary history and alterations in exercise, diet, and maturing, there is an extensive indication that environmental factors play a significant role in quickly increased occurrence of obesity, T2DM, and other facets of MetS [82].

Environmental disrupting chemicals (EDCs) belong to one of the classes of chemicals that are currently receiving much attention due to their property of interfering with metabolic hormones. These compounds are extensively being used in consumer products. Exposure to these chemicals in critical periods is of particular concern such as during differentiation of liver, adipocytes, pancreas, brain, etc. [83].

Obesity

Obesity is one of the world's most common diseases that can affect adults, children, and infants. In the past three decades, nearly double cases of diabetes have recorded in the US population [84]. It has been observed that for the first time in human history the number of cases of obesity is greater than that of the underweight cases

[85]. This remarkable increase in abdominal obesity rate has been analyzed in both developing and developed countries [86, 87]. The rate of obesity both in children and adolescents has increased equally [88]. The epidemic of obesity has also been observed in infants age 6 months and younger; such an outcome cannot be explained by no physical activity and food choices in this age group [89].

Type 2 Diabetes Mellitus

Diabetes mellitus (DM) has been defined by the American Diabetes Association (ADA) as: "a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [90]." DM may occur due to the loss of function or pancreatic tissue mass deduction [91]. Type 2 diabetes (TD2) which is also commonly known as non-insulin dependent diabetes or DM constitutes 90–95% cases of diabetes and occurs due to dysfunction of pancreatic beta cells and enhanced insulin resistance [84]. The World Health Organization (WHO) has observed that worldwide 347 million people are suffering from diabetes (90% of which is T2D) [92]. Children and young people have shown significant increase in diabetes prevalence in a short duration [93].

The most important T2D driving factor is obesity; 70% of the T2D risk is associated with weight gain. Obesity is related to insulin resistance that induces the production of beta cells, causing hyperinsulinemia usually in initial stages of MetS and T2D. Moreover, obesity is neither enough nor necessary for T2D occurrence; these situations can take place independently. Certainly 57% of the individuals with obesity were not having T2D and 20% of adults having T2D were not overweight [94].

Nonalcoholic Fatty Liver Disease and Hyperlipidemia

The liver is the main organ for lipid metabolism. Nonalcoholic fatty liver disease (NAFLD) is classified by additional glyceride storage in hepatocytes. Worldwide 25% population is suffering from NAFLD [95] and it accounts for 8% of children [96]. NAFLD and its more dangerous form, nonalcoholic steatohepatitis (NASH), are linked with the increasing rate of mortality related to the liver [95], and NAFLD is one of the risk factors of cardiovascular disease [97]. Hyperlipidemia is the most common condition which accounts for 69% of NAFLD cases, obesity accounts for 51% of NAFLD cases, T2D (23%) and MetS (43%) [95]. Initially, NAFLD thought to take place mostly in females [98] but growing evidence reveals that men and possibly post-menopausal women are at greater risk of having NAFLD [99]. Hyperlipidemia is raised level of triglycerides (hypertriglyceridemia), phospholipids, cholesterol (hypercholesterolemia), or a mixture of blood. Moreover, there is a connection between hyperlipidemia and NAFLD, not all patients suffering from one disease are by the other [100]. Total cholesterol levels and LDL cholesterol also

have been decreasing, and these positive changes may play a role in increased utilization and awareness of lipid decreasing medications [101]. The incidence of hyperlipidemia was 20% in adolescents and children in the USA during the period of 1999–2012 [102].

Insulin Resistance

Regarding MetS, it is considered that components of MetS originate from insulin resistance. Abnormal expression of gluconeogenic enzymes causes insulin resistance, which is represented by defects in glucose tolerance and enhanced level of fasting glucose. Hyperinsulinemia occurred when they start to produce further insulin release in the metabolic state. Transcription factors such as Srebp-1c in the liver are then stimulated by hyperinsulinemia, which causes hepatic steatosis and hypertriglyceridemia [103]. Moreover, the increased insulin production and secretion may cause the collapse and death of pancreatic β-cells and initialize T2D onset. The well-known insulin resistance form is linked with adipose tissue dysfunction and abdominal, representing a significant role of obesity in MetS.

In type 2 diabetes many cases were presented with insulin resistance. Due to satisfactory increased biogenesis and release of insulin and production of pancreatic β-cell mass, the hyperglycemia is not developed insulin resistance individuals, for example, in obese subjects, 2–5 times more insulin secretion occurs in glucose response, while in athletes 2–5 times less insulin is secreted. β-cell mass and functional adaptation are counteracted to insulin resistance which occurs during the period of puberty and pregnancy depending upon maternal hormones and sex [104, 105]. Therefore, insulin sensitivity controls function of β-cell; insulin-resistant subjects, regardless they are lean or obese, show a better response to insulin and less insulin clearance than individuals sensitive to insulin. The adaptation to the β-cell must fail to lead insulin resistance to T2D [106]. Hypertrophy and proliferation of existing cells regulate. The ability of β-cell mass and its function is increased by glucose, free fatty acids, metabolic hormones, and neuronal, however abnormal increase in glucose and lipids causes β-cell death and predisposes to T2DM [107].

In metabolic signal stability of pancreatic β-cells to assimilate responses to alter insulin sensitivity probably involves enhanced metabolism. These comprise of adipocytes signaling molecules (e.g., NEFAs signaling via GPR40) and fatty acyl-CoAs that stimulate the release of insulin through protein kinase C (PKC) and exocytotic machinery. Leptin, adiponectin, and proinflammatory cytokines, for example, monocyte chemoattractant protein (MCP-1) and TNFα, IL-6 from macrophages and other cells infiltrating adipose tissue that also play a role [107]. Glucagon is produced and released by pancreatic α-cells. Thus alternation in the function of pancreatic alpha cells also plays a role in T2D. The pancreatic alpha cell mass is not increased in T2D, causing enhanced α-to-β cell ratio; this altered ratio also contributes to higher plasma levels of glucagon and therefore to hypoglycemia [106]. For this reason, while β-cells are healthy, their adaptive responses counter balance

insulin resistance and maintain everyday glucose tolerance. However, if β-cellular dysfunction happens because of genetic causes, environmental perturbations, or both, then the individual is greater at risk of developing impaired glucose tolerance, excessive fasting glucose stages, and ultimately types 2 diabetes.

Environmental Contributions to Obesity, T2DM, and Dyslipidemia

The mark changes in diet and lifestyle that includes consumption of high energy diet, increase in dietary intake, and decrease in physical activity are secondarily linked to the global epidemic of obesity, T2DM, and MetS. Moreover, it is obvious that the possibility of these diseases is not that simple. Certainly, various environmental factors play role in the occurrence of metabolic diseases such as childhood antibiotics, lack of sleep, adenoviruses and stress [108–110], and exposure to environmental chemicals [111]. Although all the environmental factors play a role in the epidemic of metabolic diseases we have focused on EDCs (PFASs). Indeed, the current increase in metabolic diseases associates with considerable rises in environmental chemical production and exposures over the past four eras [112–114].

PAFSs Association with Obesity

Rising evidence suggests that raised BMI is not associated only with a diet rich in calories and sedentary lifestyle, but also coupled with extensive environmental exposure to "obesogens," such as perfluoroalkyl substances (PFASs) [115]. PFASs are extensively used in various products due to their high chemical and thermal stability [116]. A variety of animal studies has suggested that exposure to PFASs can impair lipids and carbohydrates homeostasis, change in the composition of fatty acid, and alter adipocyte differentiation [117], although results have been conflicting [118]. Similarly, findings of human epidemiological are various. A number of epidemiological investigations reported links between high level of PFOS or PFOA in maternal serum and enhanced BMI of offspring, the possibility of being obese, and low level of serum leptin levels in kids or adults [119]. Particularly, females are more pronounced to these effects [120]. Comparatively, other researchers have not found any association between adiposity and PFASs exposure [121]. PFASs show some endocrine-disrupting properties as they halt the metabolism of fatty acids, promote adipogenesis, change lipid homeostasis, and disturb energy balance through different pathways [122], together with peroxisome proliferator-activated receptors α/γ (PPAR-α/γ) activation [123], homeostatic disruption of thyroid hormones [124], and changes in level of estrogen and androgen [125]. Moreover, branched isomers of PFASs can more efficiently cross the placenta as compared to

linear isomers [126] and exhibit more effects on decreasing birth weight of infants [127], which is related greater chances of obesity [128].

PFASs Association with Diabetes and Oxidative Stress

Mixed evidence has been reported regarding the association of PFAS exposure and the risk of T2DM. C8 Health Project was the largest cross-sectional analysis, in which no association was found between lifetime exposure and fasting glucose or T2D [129], while plasma concentrations of different PFASs such as PFOS, PFOA, PFHxS, and PFNA were inversely related to diabetes prevalence [130]. On the other hand, a positive association was found between PFASs exposure and prediabetes, diabetes in an investigation of Wisconsin male anglers [131]. In a study of Chinese of Taiwan, a positive association of T2DM and serum PFOS was seen [132]. Underlying mechanisms that show PFASs and T2DM associations are not clear. Investigations have cleared that PFASs stimulate PPARγ and PPARα [133], which control homeostasis of energy, adipocyte differentiation and its functional regulation, glucose and lipid metabolism [134]. It has also been shown that PFASs also interfered by PPAR-independent pathways. Such as, PFOA changes the expression of liver cell proteins of human being that are controlled by hepatocyte nuclear factor 4α4α [135], which is a most important regulator of gluconeogenesis and lipid metabolism [136] and also stimulate homeostasis of thyroid hormone [137]. Current confirmation from in vitro investigations has additionally shown estrogenic and antiestrogenic properties of PFASs [138]. Moreover, PFOA enhances mitochondrial dysfunction and oxidative stress that cause cytotoxicity and apoptosis in rat β-cell-derived RIN-m5F cells [139]. The sub-chronic effects of PFASs exposure included the disturbed homeostasis of thyroid hormone, body weight gain and liver toxicity have been observed in experimental animal studies [17]. Further latest studies have reported that PFOS exposure in perinatal stages in rats causes abnormalities in the homeostasis of glucose and lipid at adulthood [140]. Furthermore, adult mice treatment with PFOA for 4 weeks interfered with the metabolism of glucose and insulin hypersensitivity induction [141]. In vivo study in mice exhibited that PFOA produced histopathological alternations in the pancreas by enhancing oxidative stress [142]. Abnormal development of the pancreas in zebrafish observed after PFOS exposure [143]. A strong correlation was not observed between levels of PFAS and markers of diabetes risk, for example, insulin or HbA1c, adiponectin. Human cross-sectional studies have revealed a strong connection between exposure to the PFAS and changes in liver or thyroid functions [144]. Hence, defective liver or thyroid functions may also have a role, while estrogenic effects and increased oxidative stress illustrated the PFASs–T2DM links. Moreover, PFASs may have strong effects among those individuals who are at high diabetes risk (such as overweight) or change in weight during childhood and puberty [145].

Long-Range Atmospheric and Marine Transport

A number of monitoring studies in the world have found the occurrence of PFASs in water, air, biota, and soil in far-flung areas, e.g. the Arctic [146]. Long-range transport of ionic PFASs, for example, the sulfonic and carboxylic acids (PFSAs and PFCAs), occurs most of the time through the aquatic environment, and sometimes via oceanic currents. Whereas the long-range transport of neutral PFASs, for example, the precursors called fluorotelomer alcohols (FTOHs), happens through the atmospheric route [147]. They possess properties helping in long-range transport by allowing enough residence time in the atmosphere and simultaneously they are so reactive that they are easily convertible into carboxylic acids and other products such as fluorotelomer species by undergoing oxidative reactions [147].

A study performed on the marine samples taken from the east coast of Greenland demonstrated the presence of PFAS concentration in 150–250 pg/L range. The most important single constituent of total PFAS was found to be PFOA with other short-chain PFAS, for example, PFBS, PFHxA, and PFHxS also being found. Short-chain PFASs accounting for about 50% of the total amount of PFAS were found in samples taken from closer to the coast. In contrast to this, PFOS was found abundant in samples taken from distant to sea. So, short-chain PFSAs can have long-range transport to distant areas via water. However, the sub-component of the study performed along the Atlantic transect showed continuously decreasing the concentration of PFAS in the water samples moving in southern direction from English Channel (>500 pg/L) towards the Equator (<100 pg/L). In the south of the equator, minimal PFASs were detected in the samples [148]. A recent review by ENVIRON in 2014, comprising of several monitoring studies showed the presence of 6:2 FTOH in distant areas. A transformation product of 6:2 FTOH, namely PFHxA was found in far environments that showed its capability of long-range transportation [149].

Conclusion

Perfluoroalkyl substances (PFAS) comprise a group of extremely fluorinated aliphatic chemicals that contain one or more C atoms on which all the hydrogen substituents have been exchanged by F atoms. PFASs are commonly used in several consumer and industrial goods. They are found everywhere, i.e. soil, air, and water. PFASs have drawn much attention and certain PFASs are regulated or voluntarily limited owing to bioaccumulation potential and their omnipresence in human blood. Numerous experimental studies have suggested that PFAS are linked with metabolic disorders including obesity and insulin resistance. Their chronic exposure may impair lipids and carbohydrates homeostasis, change in the composition of fatty acid, and alter adipocyte differentiation and adipokine secretion. Additionally, they also disturb thyroid hormone balance and show the estrogenic properties. These hazardous effects are partially due to increased oxidative stress induced by

PFAS. Besides of it, PPAR α/γ is considered as major target of these chemical substances accountable for the disruption of glucose and lipid metabolism. In addition to the human, they are also taken as major thread to aquatic life owing to their massive accumulation in water bodies.

Conflict of Interest The authors declare that they do not have any conflict of interest for this book chapter.

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Chapter 19
Role of Polycyclic Aromatic Hydrocarbons as EDCs in Metabolic Disorders

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Abstract Polycyclic aromatic hydrocarbons (PAHs) are universal toxic chemicals produced mainly due to improper combustion of organic substances like wood, coal, petrol, oil, etc. Release of these pollutants into the environment is because of various activities including open air burning, natural losses, leakage of various chemicals, accidental fire, and many more. The most common sources of PAH production are household heating systems, plants using coal for gasification and liquefaction, various industries and factories manufacturing different livelihood products, petroleum refineries, and automobile exhaust. In the environment, PAHs exist in gaseous-phase and sorbet to aerosols. The movement of PAH from atmosphere to humans is strongly dependent on its phase in the air and the route of entry to human body. Soil and water are the main sources of PAHs deposition in the ecosystem. Many PAHs act as endocrine-disrupting chemicals (EDCs) having a strong blow on the regulation of endocrine dependent functions including metabolism, growth, reproduction, immune system, and may also have toxic and carcinogenic properties. After exposure, PAHs enter into the human body through different routes, get absorbed, and metabolized via cytochrome P450 oxidation system. PAHs are obesogens causing dysregulation of hormonal network controlling appetite and endocrine tissues which changes insulin sensitivity and lipid metabolism. The time of obesogens exposure (prenatal, postnatal, early childhood, and young) possesses

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different consequences on the entire life span of an individual. Different assays are used to check PAHs both qualitatively and quantitatively in various samples.

Keywords Polycyclic aromatic hydrocarbons · Ecosystem · Endocrine-disrupting chemicals · Obesogens

Introduction

The endocrine system is a large network of hormones whose function is to regulate multiple cells functions harmoniously. Hormones are needed in a very minute amount and at a particular instant to control different functions of the body. This complex network has numerous stimulation points and retro-action loops in chains to set various physiological parameters including lipedema, glycemia, hydro-mineral regulation, etc. and physiological functions, e.g. development, growth, reproduction, etc. at a suitable range to maintain body homeostasis and survival of the species.

Endocrine-Disrupting Chemicals (EDCs)

Environmental contaminants that disturb hormonal system are named as endocrine-disrupting chemicals (EDCs). Scientifically, EDCs are exogenous substance or mixture that restrains or stimulates any hormonal actions. EDCs were defined by WHO in 2002 as "an exogenous mixture or substance that changes endocrine system function(s) and accordingly results in abnormal health issues in whole organism, or in its descendants, or (sub)populations." EDCs are natural or synthetic molecules that interfere and provoke harmful dysregulation of hormonal parameters or functions which are controlled physiologically [1].

Effect of EDCs on Endocrine System

Endocrine disruptors combat and interfere with the physiology of endocrine systems (hormones), and thus results in the hazardous effects which occur for a long time although the exposure has stopped. Endocrine disruptors have long lasting effects on survival and can even have obvious consequences on the next generation. According to WHO, most of potential EDCs are synthetic and are components of numerous materials including additives or contaminants in food, pesticides, personal care products, and metals. Exposure of human beings occurs via ingestion of EDCs contaminated food, drinking water, and dust particles, via inhalation of

polluted gases and their residues in the air and also through direct skin contact. EDCs transfer can also occur through placenta and breast milk from the pregnant woman to the developing fetus and to the young child, respectively.

Different mechanisms are involved which interfere functions of the endocrine system either by direct binding to hormonal receptors causing stimulation or inhibition of downstream cellular pathway of target cells or indirectly by increasing or decreasing endogenous hormone(s) concentration. Therefore, this results in the stimulation or inhibition of their bio-availability or degradation [2, 3]. Although there are a lot of potent and most available classes of environmental chemicals which are been studied but here in this chapter we have focused only on those which are polycyclic aromatic hydrocarbons in nature.

Polycyclic Aromatic Hydrocarbons (PAHs)

Organic compounds which are composed of aromatic rings (two or more) arranged in various configurations are termed as polycyclic aromatic hydrocarbons [4], mostly white, colorless, or pale yellow solids. Generally, structural angularity, hydrophobicity, resistance to biodegradation, electrochemical stability, persistency and carcinogenic index of PAHs is directly proportional to the number of aromatic rings, while volatility of PAHs has inverse proportionality with that of molecular weight [5].

Sources of Polycyclic Aromatic Hydrocarbons

PAHs are universal environmental contaminants/pollutants produced primarily as a result of incomplete combustion of organic substances such as coal, oil, and petrol. Predominantly, PAHs are released from anthropogenic activities; however, some originates from natural sources in the environment including open air burning, seepage or natural losses of coal/petroleum deposits, and volcanic bursts [6, 7]. Majority of PAHs anthropogenic sources include domestic heating system, carbon black, liquefying factories, coal gasification and tar, tarmac, aluminum and coke production, catalytic cracking posts and connected activities in petroleum processing plants and automobile exhaust. In the enclosed air, PAHs are found in gaseous stage and as ice to vaporizers. Partitioning PAHs environmental compounds (in between the gaseous and particulate phase) intensely affects their nature and movement in the environment and also by the way they get entered into the human body. PAHs removal from the environment can be made via wet and dry sedimentation processes which are intensely influenced by their gas/particle partitioning.

Environmental Polycyclic Aromatic Hydrocarbons (ePAH)

PAHs related with environmental media such as particulate matters, water, sediment, and soil are named as environmental PAHs (ePAHs), which can be divided by various methods including their sources or forms, natural hazardous effects, communal influences, and biological tests used to identify and quantify them [8]. Hundreds of PAHs are present in the environment which mostly occurs as a mixture in forms, and soil is the main source of their deposition [4]. Sixteen among them are declared pollutants of main concern by the U.S. Environmental Protection Agency, their structures are shown in Fig. 19.1 [9], some of them are also carcinogenic as well [10, 11]. ePAHs and its constituents get access into the human body through contaminated food chains, inhalation, or through skin contact and are considered as potential threats to humans [8, 12]. The source and forms of ePAHs are shown in Table 19.1.

In the environment, water, soil, air, smoke, dust, sediment, oil and/or pollutants, particulate matter, and materials in oven, fuel, and tar are different sources of PAHs. Incomplete combustion process of carbonaceous products like coal burning, forest fire, exhaust fumes of automobiles, fossil fuels and biomass including emissions from coke, cooking and heating in countryside, and tobacco smoke are the major

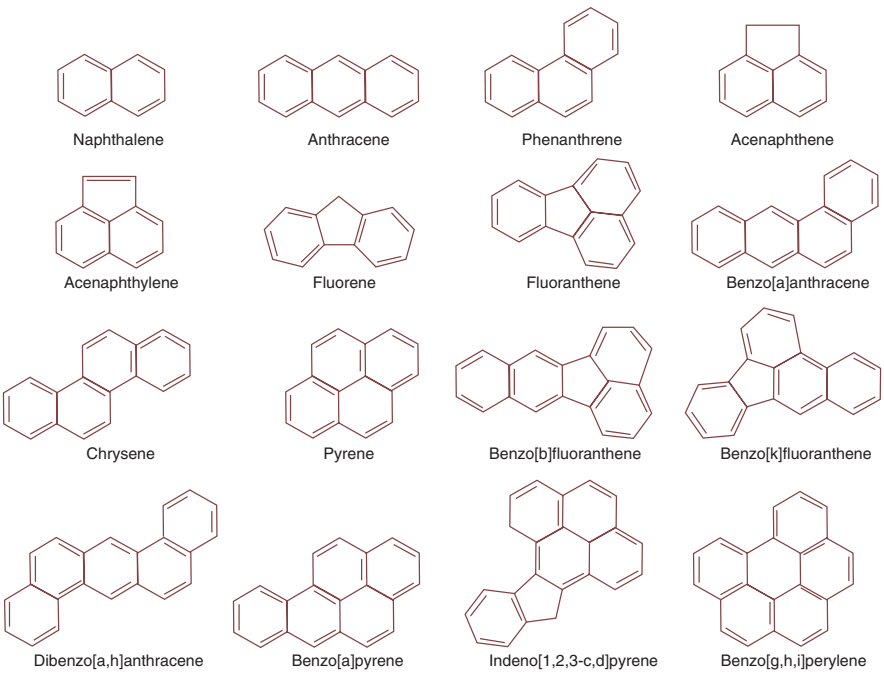

Fig. 19.1 Structure of the 16 priority PAHs pollutants enlisted by US EPA. On the basis of their abundance in the environment and their most toxic effect on humans and are thus highlighted as priority PAHs pollutants

Table 19.1 Properties and significant information of 16 US EPA enlisted PAHs as priority pollutant

Name	Mol. formula	Physicochemical properties				Toxicology			Biodegradation	
		Boiling point (°C)	Melting point (°C)	Vapor pressure (mm Hg at 25 °C)	Solubility (mg/L)[a]	TEF[b]	IARC[c]	EPA[d]	Estimated half-lives (days)[e]	Measured half-lives (days)[f]
Naphthalene	$C_{10}H_8$	218	80.2	8.5×10^{-2}	31	n.d.	2B	C	5.66	n.d.
Acenaphthene	$C_{12}H_{10}$	279	93.4	2.5×10^{-3}	3.93	0.001	3	D	18.77	n.d.
Acenaphthylene	$C_{12}H_8$	280	91.8	6.68×10^{-3}	1.93	0.001	n.c.	D	30.7	n.d.
Anthracene	$C_{14}H_{10}$	342	216.4	6.53×10^{-6}	0.076	0.01	3	D	123	2.7
Phenanthrene	$C_{14}H_{10}$	340	100.5	1.2×10^{-4}	1.20	0.001	3	D	14.97	5
Fluorene	$C_{13}H_{10}$	295	116–7	6.0×10^{-4}	1.68–1.98	0.001	3	D	15.14	n.d.
Fluoranthene	$C_{16}H_{10}$	375	108.8	9.22×10^{-6}	0.20–0.26	0.001	3	D	191.4	9.2
Benzo[*a*]anthracene	$C_{18}H_{12}$	438	158	4.11×10^{-3}	0.010	0.1	2B	D	343.8	>182
Chrysene	$C_{18}H_{12}$	448	254	6.23×10^{-2}	1.5×10^{-3}	0.010	2B	B2	343.8	n.d.
Pyrene	$C_{16}H_{10}$	150.4	393	4.5×10^{-6}	0.132	0.001	3	B2	283.4	151
Benzo[*a*]pyrene	$C_{20}H_{12}$	495	179	5.49×10^{-9}	3.8×10^{-3}	1.0	1	D	421.6	11
Benzo[*b*] fluoranthene	$C_{20}H_{12}$	481	168.3	5.0×10^{-7}	0.0012	n.d.	2B	B2	284.7	n.d.
Benzo[*k*] fluoranthene	$C_{20}H_{12}$	480	215.7	9.7×10^{-10}	7.6×10^{-4}	0.1	2B	B2	284.7	n.d.
Dibenzo[a,h] anthracene	$C_{22}H_{14}$	524	262	9.55×10^{-10}	5.0×10^{-4}	n.d.	2A	B2	511.4	n.d.
Benzo[g,h,i] perylene	$C_{22}H_{12}$	500	277	1.0×10^{-10}	2.6×10^{-5}	n.d.	3	B2D	517.1	n.d.
Indenol[1,2,3-cd] pyrene	$C_{22}H_{12}$	536	161–3	1.25×10^{-3}	0.062	n.d.	2B	B2	349.2	n.d.

[a] [93]

[b] Toxic equivalent relative factor to benzo[a]pyrene

(continued)

Table 19.1 (continued)

[c]International Agency for Research on Cancer Classification Monographs Volume 1–111 updated 18 February 2015 (*1* carcinogenic to humans, *2A* probably carcinogenic to humans, *2B* possibly carcinogenic to humans, *3* not classifiable as carcinogenic to humans, *n.c.* not classified)

[d]EPA carcinogenic classification: *A* human carcinogenic, *B1 and B2* probable human carcinogenic, *C* possible human carcinogenic, *D* not classifiable as to human carcinogenicity, *E* evidence of non-carcinogenicity for humans

[e]Estimation using BioHCwin software v1.01 on EPI Suite software developed by [94]

[f][95]

n.d. not determined, *n.c.* not classified

Various physical and chemical properties along with carcinogenic efficacy based on the comparison of toxic equivalent relative factor (TEF) with benzo[a]pyrene, the most common isoform of benzopyrene which forms carcinogenic and mutagenic metabolites

sources from which PAHs can originate [6, 13, 14]. As they are semi-volatile in nature and based on their molecular weights, PAHs may occur either in a particulate or gaseous form in the environment [15]. Water and soil are predominantly contaminated due to atmospheric PAHs deposition, particularly in distant areas including lakes located at high-altitudes [16–18], or the waste produced from industrial process which gain access to the water resources. In marine environment, noticeable sources of PAHs are oil spills, which are deposited in sea as residues. Beside biological degradation, the fate of PAH in environment depends on various other factors, such as in air soil and water, PAH can go through photo-oxidation, photo and chemical oxidation, respectively. Moreover, some PAHs, for example, naphthalene and alkyl naphthalene, are moderately vanished by vaporization [19].

Exposure of Humans to ePAHs

Living organisms possibly exposed to environmental PAHs through multiple ways result in various biological and social effects. Studies have shown relationship between water and sediments contaminated with PAHs which induce cytochrome P450 (CYP), elevate 7-ethoxyresorufin-O-deethylase (EROD) properties, damage DNA, rupture lysosomal membrane, and cause endocrine and reproductive failure in fish and invertebrates. Atmospheric and soil PAHs are also taken by the plants which cause injuries to their leaves, reduce biomass, and various other harmful biological and physiological effects. Moreover, soil microbial community composition is also influenced strongly by soil PAH contamination level. Humans become exposed to ecological PAHs via PAH-contaminated diet intake including accidental ingestion of dust and soil through hand-to-mouth behaviors, skin contact, and inhalation [20–22]. Epidemic studies have shown that from occupational environments, PAHs heavy exposure elevates cancer development risks including skin, larynx, lungs, and bladder cancers [23–25]. Cancer causing mechanism of PAHs is related with their capability to produce reactive diol epoxide which is quickly catalyzed by CYP, regulated through PAH exposure, and their consecutive binding covalently to DNA [26–28]. PAHs in non-occupational settings have been considered as etiological agents for both cardiovascular and cardiopulmonary disorders. From both in vitro and in vivo studies, it has been proposed that ROS (reactive oxygen species) are associated with PAHs in ambient particulate matter, causing inflammatory responses and oxidative stress, necessary for the occurrence and aggravation of asthma and hypersensitive diseases. Moreover, long term exposure of low-dose PAHs can cause immune-mediated pregnancy loss, and PAHs exposure in pregnancy affect fetal development including birth weight, size, length, and circumference of the head. It has been estimated that each gram of tobacco contains a total of 100 ng of PAHs, irrespective of the manufacturing industries [29], and from 20 cigarettes pack, a smoker inhales 0.26 lg of BaP [30]. Smokes from the vehicles and household fire are the main sources of PAHs [11]. Barbecued, grilled, or smoked

meat products also contain significant quantity (0.1–20 mg/kg; up to 100 mg/kg) of PAHs [31–33].

Effect of PAHs on Various Enzymatic and Metabolic Pathways

Most aryl hydrocarbon receptor (AhR) is stimulated by PAH isomers which principally act as an activator to stimulate various biochemical and toxic responses, including the regulation of cytochromes P450 (1A1 and 1B1), which leads to toxic transformation of the cell and thus develop cancer [34–36]. Moreover, some PAHs affect endocrine system by inducing ovarian estrogen receptor b expression and peroxisome proliferator-activated receptor alpha (PPARa) and delta (PPARb/d) activation. TCA cycle and purine metabolism are highly disturbed due to PAH exposure [37–39].

Excessive exposure of PAHs mostly causes lung cancer, resulted due to induction of metabolic enzymes including cytochrome P450 (CYP) monooxygenases, i.e. CYP1A1/2 and 1B1, and phase II enzymes including aldo-keto reductases (AKRs), NADPH quinone oxidoreductases (NQOs), UDP glucuronyl transferases, glutathione S-transferases, and epoxide hydrolases (EHs), by entering into the lungs via aryl hydrocarbon receptor (AhR)-dependent and independent pathways. PAHs metabolism produce active carcinogens, diol epoxides, radical cations, and o-quinones using CYP1A1/1B1/EH, CYP peroxidase, and AKR pathways which leads to produce reactive DNA adducts, results in DNA mutations and change in the downstream gene expression profile, ultimately leads to the development of cancer. Mutations in xenobiotic metabolic enzymes, tumor suppressor genes (e.g. p53) and genes responsible for cancer susceptibility from various age groups, ethnicities, and gender [40].

Endocrine and Endocrine Disruptors

In the regulation of fats, carbohydrates, and proteins metabolism, endocrine system plays a crucial role to provide fuel to the body in the form of energy, all the times. When the availability is more, endocrine hormones are accountable to mobilize and store excess energy in the form of fats in various parts of the body. During scarcity or unavailability of energy sources, this stored energy is mobilized again to compensate need of the body and most importantly to maintain constant blood glucose level. An imbalance between these two processes occurs whenever there is change in hormones secretion or production to drive the processes of metabolism.

PAHs and Metabolic Pathways

PAH metabolic pathways and metabolic enzymes are very much complex and that is why in vitro studies may not be appropriate to induce PAH metabolism and to study the exact mechanism of PAH carcinogenesis in vivo [41–43]. Nevertheless, the advantages of in vitro models cannot be ignored and are still used to determine different/single metabolic pathway, interactions of signaling pathways, gene expression including cell biology, and promoter methylation in PAH carcinogenesis. Mice models using knock-down genes have arisen as crucial tools to find out the action of a specific gene in PAH activation [44–46].

PAH Activation by Cytochrome P450s

Everyday exposure of humans to various xenobiotics leads to activate CYPs, which accounts for 75% of the total metabolic enzymes [47] and are also the main metabolic catalytic enzymes responsible to oxidize organic substances such as PAHs. All the isoforms of CYP1 are monooxygenases, which donate an oxygen atom to produce oxidative epoxides [48]. CYP1A1, CYP1A2, and CYP1B1 belong to the family of CYP1 which has a crucial part in PAH activation [49, 50]. Many studies have demonstrated that PAHs are catalyzed faster by CYP1A1 compared to other isoforms of CYP1 like CYP1A2, 2C9, 3A4, and 2C19. Remaining isoforms may not have a role in PAH metabolism including CYP2A6, 2B6, 2C8, 2D6, 2E1, 3A5, 3A7, and 4A11 [51, 52]. Instead of CYP1A2, endogenous CYP1A is found in lungs and is extremely inducible by PAHs [53, 54]. The stimulation by PAHs may continue for several days or even months, even though the exposure of PAHs has stopped long before [43, 55, 56], which is considered an important phenomenon for cancer development [57].

Obesogenic EDCs

Fats are the major form of stored energy in the body preserved in adipocytes in the adipose tissue, and the adipose tissue has been recognized to be controlled by the endocrine system and may also work as an endocrine organ because of having the ability to secrete hormones [58]. Interference in hormonal regulation of adipose tissue functions leads to an inappropriate deposits of fat which causes obesity (Fig. 19.2). Reports are increasing which showed that some EDCs may also hamper the control of metabolic processes and adipocyte function, resulting in an imbalance in the body weight regulation, which can cause obesity [59–61]. Such chemical which causes obesity has been named “obesogens” [62, 63]. 30 kg/m^2 body mass index is considered obesity which has become a universal problem over recent

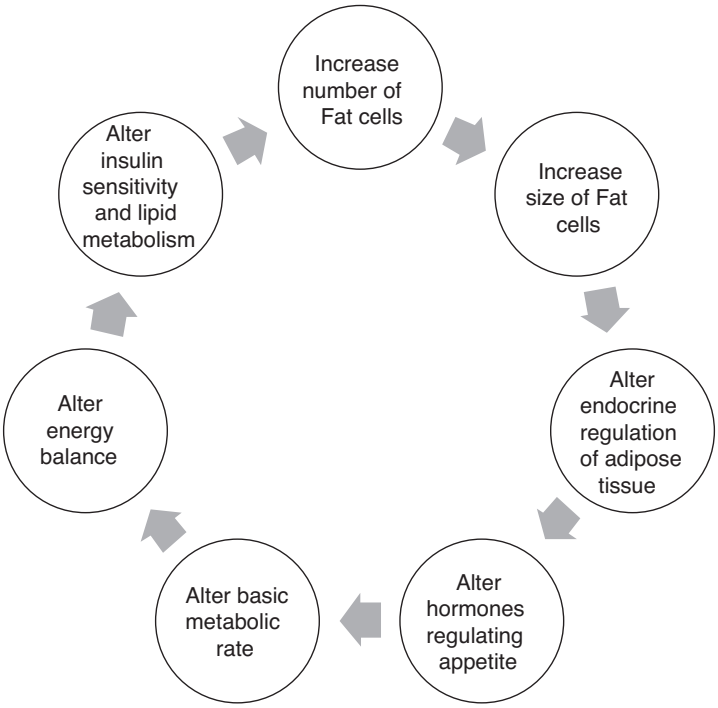

Fig. 19.2 Obesogens mechanism of actions to alter lipid homeostasis which results in obesity. These are the possible enlisted mechanisms which PAHs (obesogens) can adopt and cause obesity

years. Around 20% of children [3–17] are obsessed and are increasing in faster rate in western countries and in the USA. The neonatal and in utero period are the more sensitive time period for obesogens [64].

Mechanisms of Action of Obesogenic EDCs

Obesogens stimulate adipogenesis, altering lipid homeostasis and lipid accumulation, resulting in weight gain which occurs through several mechanisms, as shown in Fig. 19.2, which may include increase in both numbers or size of adipocytes, alteration in the endocrine pathways that govern adipose tissue development. Generally, an increase in adipocyte number occurs during early developmental changes (embryonic and postnatal), while a surge in the size of adipocytes occurs mainly during adulthood. This evidence verified that at the end of childhood, adipocyte numbers are set and in early life the number of adipocytes tends to be permanent [65]. So the time of obesogens exposure has profound consequences suggesting that changes in the initial life period would pass on into maturity and would not be retreated [60]. Alteration in endocrine hormones that normalize hunger, satiety, and

selection of food results in the alteration of basal metabolism or the energy equilibrium to favor reserve calories. Last but not least, alterations in endocrine tissues including liver, brain, pancreas, adipose tissue, or gastrointestinal tract which alters insulin sensitivity and lipid metabolism also may have involvement.

Genetically, obesogens work just by regulating nuclear transcriptional factors that further regulate lipid change and/or adipocyte differentiation/multiplication, such as PPARα, PPAR-δ, and PPAR-γ (peroxisome proliferator-activated receptors) and steroid hormone receptors. After binding to ligands these receptors work as ligand-activated transcription factors, which with the help of response elements binds to DNA and regulates precise patterns of gene expression [66].

Parental Exposure and Early Childhood Obesity

There are multiple reasons for childhood obesity, starting from the individual level such as behavioral risk aspects including high fat consumption, working behavior, and time duration, and societal-level risk aspects which determine diet and physical activity such as agricultural policies, suburbanization, and mechanization [67–69]. However, there is an interesting emerging theory which states that exposure in early life (4–10 years) to environmental endocrine disruptors has a crucial role in altering metabolic programming that causes obesity. Prenatal exposure to enclosed PAHs environment showed to have high BMI z score which suggests obesity at the age of 5 and fat mass at the age of 7 years. The effect due to PAHs when exposed in prenatal life on fetal body size is due to the addition of fat mass without any alteration in lean mass. Pregnant women kept in controlled environment monitored for PAH exposure, 21% and 25% at age 5 and 7 years, respectively, were found obsessed [70]. Obesogens (endocrine-disrupting chemicals) promote adipogenesis that causes weight gain [71].

Mechanism of Toxicity of PAHs

PAH toxicity was initially investigated by John Hill in 1761, a known medical practitioner who in tobacco snuff consumers founded nasal cancer in a high incidence rate [72]. Low-molecular weight PAHs (composed of two or three aromatic rings) showed acute toxicity, while high molecular weight PAHs (four or more rings) are found to be genotoxic [73, 74]. It has been verified that PAHs bind covalently to DNA, RNA, and proteins, but the carcinogenicity lies in the covalent interaction of PAHs to DNA only [5, 75]. Moreover, the toxicity of daughter products is more compared with parent PAHs which can result in critical cellular effects [76]. Monooxygenase group of enzymes in humans cytochrome P450 (as discussed above in detail) converts PAHs to epoxides, some of which (like “bay-region” diol epoxides) have high reactivity and is named as crucial carcinogens. Such epoxides

when bind to DNA cause transformation of normal cells to malignant one [77, 78]. It has been confirmed that food prepared at high temperatures (such as barbecuing or grilling) results in high levels of PAHs. The interest and consequences related with PAHs have been increased because of their capability to hamper the activity of hormone metabolizing enzymes which results in harmful effects on the reproduction as well as immunity [79, 80].

PAHs and Carcinogenic Pathways

In general, PAHs belong to lipophilic compounds which have the property to easily cross plasma membranes via passive diffusion post-inhalation, ingestion, or skin contact. PAHs parental molecules that gain access are considered pro-carcinogens because they cause an indirect damage to DNA molecule [81–83]. Instead, transformed carcinogenic metabolite of a single PAH contributes to cancer etiology. This transformation involves various metabolic enzymes which mostly follow three known pathways: the CYP/EH pathway (CYP1A1/1B1 and epoxide hydrolase pathway), CYP peroxidase pathway, and AKR pathway (aldo-keto reductases pathway). Generally, metabolic enzymes such as CYPs metabolize PAHs into quinones, phenols, and catechols which results in diol epoxides, radical cations, or reactive and redox-active o-quinones formation, which further reacts with DNA to form DNA adducts. For instance, quinones react with the N-3 of adenine and N-7 of guanine of DNA [84]. These DNA adducts result in incompatibility in DNA duplication, transformed promoter methylation as well as promoter binding [85] and hence leads to hereditary DNA mutation or atypical gene expression level, which ultimately results in cancer development. Though PAHs are supposed not to cause hepato cancer, but they are break down to reactive DNA metabolites in hepatocytes subsequent oral consumption [45]. PAHs reactive metabolites also enhance protein adduction in cells [86, 87], which further regulate the usual function of the proteins. PAH metabolites also result in increased production of reactive oxygen species (ROS), which directly damages the structure of DNA, lipids, or proteins and thus initiates carcinogenesis [88].

Tests Used to Determine the Biological Activity of PAHs

The following are some of the assays which are very commonly used to evaluate the biological effect of PAHs especially ePAHs from various samples.

Microbial Tests

Microbes, especially bacteria (*Salmonella*) are most frequently used in vitro to study the biological properties of PAHs. Based on the mutation properties, Ames test and umu test are widely used to screen out carcinogenic and mutagenic PAHs and ePAH, respectively. *Salmonella typhimurium* forms colonies in histidine specific agar plates when exposed to chemicals. Mammalian microsomal enzymes are added to increase the metabolic activity as some carcinogenic chemicals need metabolic enzymes to be activated. After the carcinogens were activated, the DNA damage is quantitated based on the β-galactosidase activity using colorimetric assay [89]. Chemiluminescence assay, in which luminescent bacteria produce light when exposed, is also used in the microbial test to check the biological activity of PAHs. The LUMIStox, ToxAlert, and Microtox bioassays are also based on similar principles in which a decrease in the luminescence rate by PAHs toxicants is quantified by the decrease in the respiration rate of bacteria used [90]. These are the most common tests used to check various biological effects of PAHs, the results are highly variable depending on the assay used, specificity, durability of chemicals, and sensitivity of test but the advantages of these assays are that they are less expensive and less time-consuming.

In Vitro Cell Assay

Different types of cells are used to detect the adverse biological activities of PAHs; luciferase gene expression assay is frequently used to detect the PAHs in various samples including water, soil, sediments, etc. To check DNA damage and its repair, migration with high sensitivity and specificity, comet assay is used. Flow cytometry is also the simplest and widely used assay in cell lines to significantly check chromosomal damage and genotoxic property of PAHs [91].

Plasmid Vector Reporter Gene Assay

Various plasmids or recombinant yeasts are constructed which acts as a vector, equipped with different kinds of reporter genes for biological markers (both for proteins and genes) which bind to their corresponding receptors or ligands and the biological activity of PAHs is quantified by molecular based studies. Biological effects such as estrogenicity, carcinogenicity, toxicity rate, and some other activities of PAHs are used using different cell lines and reporter genes.

Enzymatic Tests

Different kinds of enzymatic tests are used to analyze both qualitative and quantitative effect of PAHs, such as Western blotting, mass spectrometry, enzyme linked immunosorbent assay, and immunohistochemistry. Western blot and ELISA are the most commonly used tests to quantify the effect of PAHs on the marker proteins, especially the endocrine disruptors PAHs [92].

In Vivo Assays

In vivo test results are different and considered more efficient compared to in vitro studies because of the involvement of biological environment and the direct interaction of metabolic enzymes. A variety of biological in vivo test are used to check the effect of PAHs on various organ systems. Xenograft mouse model is widely used to check the carcinogenic metastatic properties of particles containing PAHs as major component. Biological activities associated with the PAHs exposure such as hyperplasia and metaplasia of different cells and toxicity of different organs are evaluated through tissues and serum obtained. Chick embryo-toxicity test (CHEST) is used to check the toxicity, mutagenicity, transgenic transformation, and embryonic mortality from parents to offspring when exposed for long time to crude tar, diesel exhaust fumes containing various PAHs components. Invertebrates such as earthworm, nematodes, amphibians, polychaetes, water snails, etc. survival rates are used to evaluate the toxic and cytopathic effect of PAHs from manufacturing gas plant sites, sediments of wetlands near highways, and seawater contaminated with powdered waste coal [38].

Conclusion

Air, soil, and water are the main sources of PAHs deposition, resulted as an outcome of different natural or accidental activities on the surface of earth which are divided on the basis of their biological activity and social impact. PAHs can act as endocrine-disrupting chemicals and thus affect the normal body process which even results in obesity, toxicity, and carcinogenesis. Time of exposure and route of entry are the two main factors that determine the underlying consequences of PAHs. Both in vitro and in vivo assays are used to check the presence as well as the quantity of PAHs in different samples.

Conflict of Interest All the authors have declared no conflict of interest.

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Chapter 20
Tobacco Smoking as an EDC in Metabolic Disorders

Komal Jabeen, Muhammad Sajid Hamid Akash, Kamran Haider, Amna Faheem, Muhammad Tariq, and Kanwal Rehman

Abstract Tobacco smoking is a leading concern to a global health; kills almost six million individuals annually and associated with life-threating health issues. Nearly 80% smokers live in middle- and low-income countries where illness and mortality rate due to cigarette smoking are higher. Tobacco smoking is interlinked with a numerous disease, comprising lungs cancer, chronic obstructive pulmonary disease, infertility, cardiovascular events, stroke, and metabolic disorders. Tobacco smoking has ability to obstruct and/or interfere in the function of endocrine system; has been entitled as endocrine disrupting chemicals (EDCs). EDCs are a heterogeneous group of exogenous compounds that can restrict with several facets of endogenous hormones. Standard role of endocrine system is reliant on hormonal/enzymatic pathway which may act as chemical and biological messengers to regulate the physiological functions of an organism. Tobacco smoking is also responsible to impair the regular metabolic pathway through interaction with members of superfamily of nuclear receptor such as peroxisome proliferator activated receptor, thyroid hormone receptors, liver X receptor, and retinoid X receptor. Smoking can also affect the multiple pathways including inflammatory response, DNA damaging, and

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oxidative stress. Reactive oxygen species (ROS) work as a second messenger in miscellaneous mitochondrial and cellular procedures and signaling pathways. On the other hand, excessive ROS might react with nucleic acid, lipids, carbohydrates, and protein causing inflammation and oxidative stress that are the main causes for the development of various metabolic disorders. Hence, this chapter will include the detailed discussion about the impact of cigarette smoking on metabolic disorder along with its effects on several enzymatic and metabolic pathways.

Keywords Cigarette · Endocrine disrupting chemicals · Metabolic disorders Cardiovascular diseases

Introduction

The human beings are exposed to EDCs via several consumer, industrial, cigarette smoking as well as agriculture products, which have become global environmental pollutants (Fig. 20.1). It comprises the by-products of explosion from ships, vehicles, and aircraft, industrial chemicals; detergents which are used for cleaning in both domestic and industrial applications, plastic which are used in water bottles,

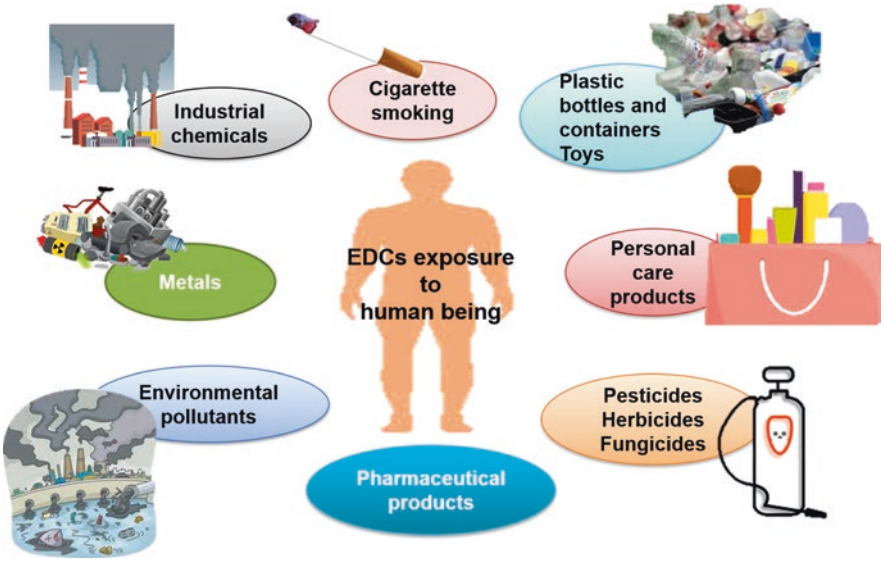

Fig. 20.1 How the human beings are exposed by the EDCs. Numerous factors such as industrial chemicals, personal care products, tobacco, cigarette, plastic bottles, containers, toys, environmental pollutants, pharmaceutical products, herbicides, pesticides, fungicides, and metals are included

food containers, and toys and finally, the components include in agriculture area are herbicides and pesticides, smoking also consist of a complex combination of compounds majorly including EDCs and it is responsible to trigger several hormone concentration in body [1, 2]. Smoking acts as EDCs that may pose the highest risk throughout pre-natal and post-natal growth and development when neural system and organs are under developing stages [3].

Tobacco smoking is the leading concern to global health; kills almost six million individuals annually and associated with life-threating health issues. Nearly 80% of smokers live in middle- and low-income countries, where illness and mortality rate due to cigarette smoking are higher [4]. The tobacco companies produce 6 trillion cigarettes in a year that are utilized by 1-billion smokers globally [5, 6]. Smoking is interlinked with a numerous diseases, comprising lungs cancer, chronic obstructive pulmonary disease, rheumatoid arthritis, infertility, miscarriage, cardiovascular events, stroke, and metabolic disorders. Tobacco consumption is one of the foremost reasons of preventable death worldwide. Consequently, metabolic disorders comprise the accumulation of numerous metabolic deformities and potentiate the risk for cardiovascular diseases and diabetes mellitus [7]. Metabolic syndrome is a multifarious disorder and it is described by a cluster of inter-connected features that ultimately enhances the risk of type 2 diabetes mellitus (T2DM), atherosclerotic as well as cardiovascular diseases. The central constituents of metabolic syndrome are including predominantly elevated arterial blood pressure, insulin resistance, glucose homeostasis, obesity along with dyslipidemia [8].

The targeted effects of smoking on health are currently well documented and recognized as it is accountable for approximately seven million deaths per year [9]. Pakistan is one of the top tobacco utilizing countries in Asia with more than 23.5 million consumers, and subsequently resulting in consumed tobacco about 90,000 tons annually [10]. Smoking usually has deleterious health events, since smoke inhalation characteristically poses risks to several physiologic procedures, such as respiration [11]. Now in Pakistan, it is predicted that the prevalence of cigarette smoking is more than 35% for men and less than 10% for women [12]. Tobacco is inhaled and consumed in various forms, such as shisha, naswar, gutka, hookah, chewing paan, and cigarettes in Pakistan. Unfortunately, the use of tobacco is increasing in Pakistan, the utilization and consumption of tobacco which has been augmenting annually. According to the State Bank of Pakistan, more than 64 billion tobacco was smoked in the year 2014 [13].

Tobacco smoke possesses both addictive and toxic ingredients. Tobacco smoke comprises nearly 7000 chemical ingredients. Most of these are harmful as well as noxious and above 60 are recognized to be carcinogenic. Several known chemicals such as benzene, formaldehyde, ammonia, carbon monoxide, vinyl chloride, and nicotine are included. Benzene can be present in gasoline and pesticides, and it is also found in larger amounts in cigarette. Vinyl chloride is used in plastics manufacturing, and smokers are uncovered to it through cigarette filters [14]. Ammonia is usually used in fertilizers and cleaning purpose and it also plays a critical role in enhancing the nicotinic effects. Admittedly, nicotine is a poison; it is an addictive chemical in cigarettes and also used in pesticides. Cigarette smoke also contains a

larger amount of carbon monoxide and hydrogen cyanide that are noxious to human health [13, 14]. Additionally, A second-hand smoker (SHS) that is also known as environmental tobacco smoker is a term that is used to define cigarette smoking that derives from binary sources, smoke that is respired by the smoker, is called mainstream smoker, and smoke that is made by smoldering cigarette also known as sidestream smoke. There is not any kind of unrestricted area of exposure to SHS which means if there is exposure of smell of cigarette smoke in the environment, it could be hazardous to human health [15].

A recent study reported that more than 55% adults and less than 35% adolescence were prone to SHS at public areas, while more than 25% childhood were exposed to SHS in their household. Media campaigns might lessen the burdens of tobacco cessation by supporting the defense and protection of non-smokers individuals and by developing the strategies for convincing the humans to discontinue the caseation of cigarette [13]. The peoples living in rural areas are more susceptible to smoke larger than 15 cigarettes each day [16, 17]. Recently, it has been reviewed that the most common reasons that are associated with initiation of cigarette smoking are stressful life events, for instance, death of loved one, job loss, educational stress, fewer availability of carrier opportunities, childhood trauma, and numerous other events [18]. Likewise, stress has crucial contribution for incidence to start smoking. Various social and psychological stress also proliferate the hazard of smoking origination [19, 20]. In this chapter, we aimed to find out the association of impact of smoking on various enzymatic and metabolic pathways that are responsible for metabolic disorders.

Human Exposure of Tobacco Smoking

Tobacco smoking that has noxious health effects in an integral organism and/or on its offspring, subsequent to alterations in the endocrine function/system. Normally, endocrine system is governed by hormones which may act as chemical messengers to control the physiological functions of the body. Tobacco smoke can reach to the tissue site owing to environment contact which is responsible to influence the numerous endogenous metabolic feedbacks. The small amount of tobacco smoke interacts with vital organs of the body for longer period of time which leads towards the chronic exposure and interferes the hormonal regulation with severe antagonistic consequences to human health [2].

Effect of Tobacco Smoking on Enzymatic and Metabolic Pathways

The cigarette consists of heterogeneous cluster of exogenous compounds that can restrict with several facets of endogenous hormones that interfere with various human metabolic and enzymatic pathways. Recently, it has been obvious that metabolic disorders cannot be entirely attributed to enhance the caloric intake, deficit sleep, and lack of physical activity and aging, among numerous environmental factors are concerned to interrupt the metabolic pathways and cigarettes have exhausted the utmost consideration of scientific community [3]. Throughout the past 50 years, the worldwide rates of diabetes, obesity, and several others metabolic and enzymatic disorders have been augmented exponentially. Actually, the predictable increases in the incidences of metabolic and enzymatic diseases coincide and correlate chronically with an increase in cigarette use. Although, evolving epidemiological data are emphasizing the close relationship between cigarette smoke and metabolic/enzymatic diseases. Animal and experimental data have proposed multiple pathways by which smoking can alter the hormonal environment and stimulate metabolic disorders [21, 22]. Smoking mainly shown noxious impact during growth and developmental duration like puberty, fetal life, progeny, pregnancy, infancy, and menopause, can deleteriously affect the persons which suffer the crowd of metabolic, enzymatic, and several other diseases [3, 23].

Standard role of the endocrine system is reliant on hormonal/enzymatic pathway which may act as chemical and biological messengers to regulate the physiological functions of an organism. Similarly, glands are the source of hormone secretion and then distribute it throughout the body with the help of carrier (blood and proteins) and then the responses are showed by the action of enzyme on the target and specific cells of the distant parts of the body. Smoking can affect the intracellular signaling, enzymatic, hormonal, and metabolic pathways that could be functional under non-genomic and/or genomic mechanisms. As a non-genomic mechanism, binding of hormone to receptor on surface of cell is considered responsible for triggering intercellular signal transduction as a result of smoking leading to deleterious effects [2].

Cigarette smoking poses a predictable risk to human health. Several studies exhibit that genital malformation, diminishing sperm count, and elevating the deleterious/undesirable impact on reproduction caused by the disclosure of EDCs. Increased utilization of cigarette not only alter the reproduction but also distress the metabolism, persuade the onset of obesity, enzymatic and metabolic disorders. Smoking can affect the morphological modification and alter the molecular and enzymatic pathways. Cigarette smoke is also responsible to impair the regular metabolic pathway through interaction with members of superfamily of nuclear receptor such as peroxisome proliferator activated receptor (PPAR), thyroid hormone receptors(THR), farnesoid X receptor, liver X receptor, and retinoid X receptor [24].

Correspondingly, consumption of unclean water and food along with inhalation of environmental airborne containments and impurities demonstrates the major concern of human contact to EDCs. Cigarette smoking that can un-suitably promote

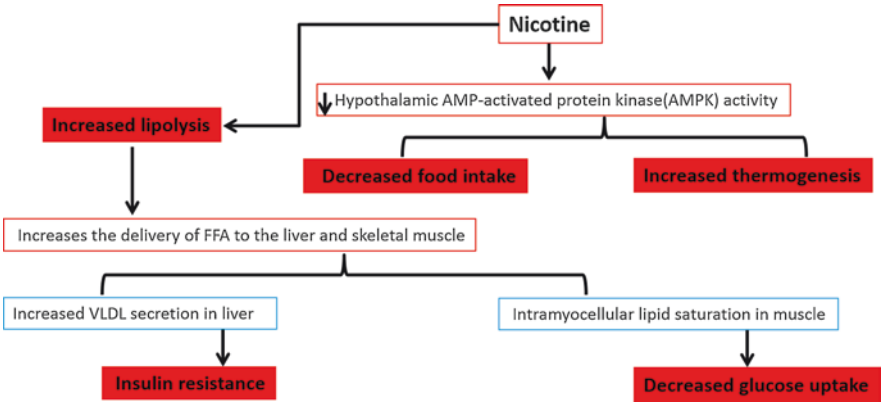

Fig. 20.2 Effects of cigarette smoking on metabolic pathway. Nicotine is an active metabolite of cigarette smoking. It obstructs the hypothalamic AMP-activated protein kinase activity which decreases the intake of food and increases thermogenesis. While on the other side, it augments the lipolysis and then surges the delivery of free fatty acids to the liver and skeletal muscle. These effects of nicotine are associated with increased very low-density lipoprotein (VLDL) secretion in the liver and intra-myocellular lipid saturation which respectively causes insulin resistance and decreased glucose uptake in muscle

and regulate the adipogenesis and lipid accumulation are called as obesogens [24–26]. In previous cascade, the list of obeso-genic chemicals that are able to disturb lipid metabolism has been significantly increased. Exposure of cigarette smoking in actual can directly enhance the number and size of adipocytes and/or indirectly impact on the hormonal regulation of appetite and basal metabolic rate [27] which may lead towards the decreased food intake and increase in thermogenesis (Fig. 20.2).

Tobacco smoking affects the endocrine system that regulates the secretion of various hormones which are responsible to control various metabolic and enzymatic pathways. Hormones mainly including androgens, estrogens, thyroid, insulin, and glucocorticoids regulate the pathways that manage the appetite, energy balance, and adipocytes. Other hormones and enzymes that can regulate the metabolism through the actions are the glucagon (GLP-1), GIT (cholecystokinin, ghrelin), muscle, pancreas (glucagon, insulin), adipose tissue (adiponectin, leptin), liver (insulin, glucagon), brain and immune system are also affected by cigarette smoke. The utmost common lipid metabolism variations/alterations occur due to subsequent exposure of cigarette, it has capability to affect circadian rhythms in addition to up regulate the EDCs expression, leading to significant elevation of lipid accumulation [28]. Tobacco has various enzymatic and hormonal alteration impacts on human health. The crucial adverse events that have been caused by the cigarette and tobacco smoke are involved in reproductive tract dysfunction, body weight variations, alteration in molecular and cellular pathway that are involved in the regulation of obesity and body weight [29].

Effects of Tobacco Smoking on Lipid Metabolism

Nicotine in cigarette is responsible to stimulate the sympathetic nervous system and suppress the catechol's which escalate energy expenditure in individuals. In serum free fatty acid (FFA) concentration is increased due to inhalation of cigarette smoke. Elevation of FFA or lipolysis may lead to the thermogenesis. FFAs are also recognized to increase the consumption of oxygen in cardiac tissues. Unwanted consequences of nicotine-induced lipolysis increase the serum cholesterol, low-density lipoprotein (LDL), triglyceride, and decrease high density lipoprotein (HDL) concentration [30, 31]. There is dose response relationship that correlates between the serum concentration of lipid profile and numbers of cigarette smoking per day [32]. In numerous dyslipidemia situation such as metabolic disorders mainly diabetes, increased distribution of FFA to the hepatic site which has been proposed to be the source of augmented the very low-density lipoprotein (VLDL) and alter the lipids profile in serum [31].

Effect of Tobacco Smoking on Carbohydrates Metabolism

Cigarette smoking and/or its metabolites mainly nicotine and various others chemicals such as cadmium and arsenic which as EDCs, are broadly spread in atmosphere and are causing an extensive range of serious health-related issues in human. After administration of these agents into the human body via either source, they all are preferably accumulated in pancreas, renal and hepatic site, where they unveil deleterious and noxious impact on carbohydrate metabolism by impairing and altering the appropriate activity of enzymes [33]. Interruption of glucose homeostasis plays a fundamental role in the pathogenesis of metabolic disorders [34]. Beside with compromised properties of pancreas, muscles, diminished hepatic and renal functions also play a considerable role to augment the level of blood glucose. Numerous studies have shown that cigarette smoking has strong relation with occurrence of metabolic disorders [34, 35]. These EDCs have probable to get conformational changes in enzymatic pathways and make them inactive. Furthermore, cigarette smoking can also impact on hormonal activity cause disturbances on the hormonal balance, for instance, catecholamines, glucocorticoids, and insulin, by damaging the pancreas and adrenal gland, respectively [33, 36].

Smoking-Induced Insulin Resistance and Impaired Insulin Secretion

The incidence of diabetes is increasing worldwide and has become a considerable health concern globally. Although in the previous era, several studies have found the associations between tobacco/cigarette smoke and disturbance in the metabolism of glucose. Insulin sensitivity and secretion both are the principal features that responsible for glucose tolerance [37]. Tobacco smoke can injure the pancreatic β-cells that lead to the impaired insulin secretion and hence, the overall metabolic pathway becomes impaired [38].

Mitochondria plays a key role in metabolic syndrome and insulin resistance. Tobacco smoking has been considered as mitochondrial function disrupter. Mitochondria are individual intracellular energy houses that generate power in the form of ATP. Mitochondrial dysfunction might be the reason of impairment of insulin secretion, glucose intolerance, and insulin resistance. The decline in the density of mitochondrial DNA in circulating blood led to the development of T2DM [39, 40]. Mitochondrial dysfunction decreases the fatty acid oxidation which results in the accumulation of intracellular fat, improved serine phosphorylation of insulin receptor by augmented production of lipid metabolites, giving rise to insulin resistant. Moreover, numerous genetic and environmental factors are involved in mitochondrial dysfunction [41, 42]. The maintenance of energy metabolism depends on the combined action of a huge count of hormones functioning that liable to maintain and control glycemia, secretion of insulin from pancreas, and insulin resistance. EDCs can interact with hormones receptors and activate the impairment of insulin secretion and resistance [43].

Tobacco smoke has influential role and pathophysiological role in the prevalence of metabolic syndrome. These factors also play a pivotal role to interrupt the insulin signaling in adipose tissue, muscle, and liver, resulting in epigenetic alterations leading to resistance of insulin and impairment of β-cells. Accordingly, metabolic distress may also accelerate the actions of EDCs. For example, excess of fat and calories in food and lack of walk may lead to the onset of obesity which is a primary for the progression of insulin resistance and impaired insulin secretion [44].

Smoking-Induced Oxidative Stress in Metabolic Disorders

Oxidative stress has been broadly recognized as potential mediator of metabolic disorders and obesity. Oxidative stress is typically defined as an imbalance between the antioxidant and oxidant species within an organism when exposed to dissimilar sources of environmental stress. Exposures of cigarette smoking as an EDC are responsible to generate inflammatory response and oxidative stress, which have been linked with insulin resistance, metabolic syndrome, obesity, cardiovascular diseases, and diabetes. Smoking can cause increased production of reactive oxygen

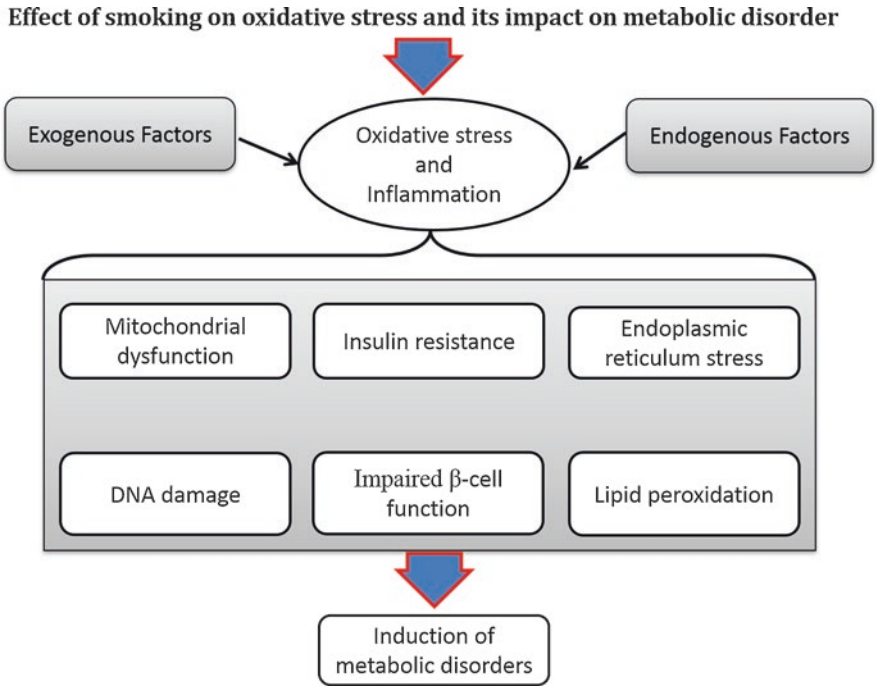

Fig. 20.3 Effect of smoking on oxidative stress and its impact on metabolic disorder. Smoking causes the generation of oxidative stress and inflammatory responses by interfering with numerous mechanisms, for example, mitochondrial dysfunction, endoplasmic reticulum stress, DNA damage, β-cells death, lipid peroxidation, and insulin resistance that are main culprits for development of various metabolic disorders

species (ROS) and others chemicals that are responsible for oxidative damage and persuade insulin resistance and oxidative stress [45]. Due to toxic chemicals such as cigarette/tobacco smoke, can develop a link between immunity, metabolic disorders, obesity, and oxidative stress in an organism, and immune system is weak and vulnerable to affect due to oxidative stress because of a proliferation of ROS production in organism [45, 46]. Oxidative stress through smoking is responsible to the generation of various antioxidant exhaustion and endoplasmic distress, cell death, mitochondrial dysfunction, and mutation in cell signaling, enzymatic and metabolic pathways (Fig. 20.3). Fundamentally, variations in mitochondrial dynamic, biogenesis, and subsequently un-necessary generation of ROS due to environmental exposure of EDCs primarily cigarette smoke, can influence the metabolic homeostasis and also contributes to the development of insulin resistance and consequently T2DM [47, 48]. Cigarette smoking can affect the multiple pathways including inflammatory response, DNA damaging, and oxidative stress. ROS work as a second messenger in miscellaneous mitochondrial and cellular procedures and signaling pathways. On the other hand, excessive ROS might react with nucleic acid, lipids, carbohydrates, and protein causing and inflammation and oxidative stress that are the main cause for the development of various metabolic disorders [49–51].

Several investigations have proven that exposure of smoking can cause the damaging effect on mitochondrial function. EDCs likewise cigarette smoking and tobacco smoke have been revealed to enhanced in vitro stress in endoplasmic reticulum and in vivo concerning liver, kidney, and pancreas. Oxidative stress is reported by production of ROS and contributes to developing T2DM by destruction of pancreatic β-cells endoplasmic stress and mitochondrial dysfunction has augmented the risk of oxidative stress. Increased oxidative stress can also initiate and trigger numerous inflammatory responses/pathways and amplified the risk of generation of various metabolic disorders, for example, obesity, diabetes, and insulin resistance [52, 53].

Tobacco Smoking-Induced Inflammatory Response in Metabolic Disorders

Cigarette smoking acts as EDCs and is documented as a risk factor for initiation of various inflammatory responses that lead to the development of metabolic disorders. Cigarette smoking can vary the pancreatic functioning by disturbing the physiology of both glucagon and insulin secretory cells, which could more distress the regulation of lipid, carbohydrate, and protein metabolism. Loss of β-cells mass by contact of cigarette smoking is primarily directed by several pathways that are linked in endoplasmic reticulum stress, mitochondrial dysfunction, inflammation, and oxidative stress. Endoplasmic stress in several cells plays a significant part in the pathogenesis of numerous diseases, including T2DM, chronic obstructive pulmonary disease, intestinal bowel disease, and cancer, and ES-induced inflammatory pathways disruption can contribute to markedly progression of such diseases. Endoplasmic reticulum stress shows a dominant role in apoptosis of pancreatic islets and causing death of β-cells that may lead to the development of various metabolic disorders [54].

Conclusion

In this chapter, we have briefly discussed the impact of tobacco smoking on the pathophysiology of metabolic disorder that can be considered as major cause of morbidity and mortality globally. Nowadays, the cigarette smoke can chiefly restrict with several facet of endogenous hormones and also interrupt metabolic and enzymatic pathways. Cigarette smoke can also distress carbohydrate and lipid metabolism and induced obesity, insulin resistance and impaired insulin secretion. Further studies are needed to investigate the underlying mechanism by which cigarette smoke which can cause metabolic disorder and developed the therapeutic interven-

tion against cigarette/tobacco use that can further improve the patient's outcome by using appropriate strategies.

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Conflict of Interest Nothing to declare.

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Chapter 21
Role of Pharmaceuticals as EDCs in Metabolic Disorders

Arruje Hameed, Tahir Farooq, and Sadia Shabbir

Abstract The endocrine system consisting of hormone producing endocrine glands and their receptors; do control, coordinate, and regulate a variety of crucial physiological functions in human body. The hormones, the chemical messengers which are secreted directly into circulatory system regulate body's growth and development, embryonic development, and primary sex characters, etc. The endocrine system manages to regulate glucose and lipid metabolism. However, it has been observed that a number of exogenous chemicals could interfere with the normal functioning of the endocrine system; disrupt the hormonal-synthesis and secretions, their transportation process and binding properties, and finally their physiological actions. Thus, they are termed as endocrine disrupting chemicals (EDCs). Unfortunately, such EDCs are ubiquitous in nature and move passively into human body through various unavoidable routes. They include but not limited to environmental toxicants, pesticides, herbicides, and pharmaceuticals. These EDCs impair the normal functions of hormones and the adverse effects are observed in the form of neurological disorders, sexual abnormalities in both genders, psychological and behavioral issues. They also cause metabolic disorders leading to obesity and type 2 diabetes. This chapter focuses on pharmaceutical products as EDCs and their role on incidence of insulin resistance and obesity. The pharmaceutical products could act as EDCs when they get discharged directly from pharmaceutical industries into environment through untreated wastewater. So, they could act as EDCs when they end up in normal human body through various routes and means. Secondly, the pharmaceutical products act as EDCs when they are used as medications for treatment of diseases but they show some undesirable off-target interaction with the endocrine system.

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Keywords Insulin resistance · Lipid metabolism · Endocrine disrupting chemicals · Metabolic disorders

Introduction

A number of very crucial physiological functions in human body are controlled, coordinated, and regulated by the endocrine system which consists of hormone producing endocrine glands and their receptors. The important roles of endocrine system include regulation of glucose and lipid metabolism, body growth and development, embryonic development, and primary sex characters, etc. These physiological functions are controlled and coordinated by the hormones; the chemical messengers secreted directly into the circulatory system. However, it has been observed that a number of compounds do interfere in the normal functioning of the endocrine system by disrupting the hormonal-synthesis and secretions, their transportation process and binding properties, coordinated and well-mechanized actions [1]. Resultantly, such non-targeted interacting compounds inhibit or enhance the functional properties of hormones, thus termed as endocrine disrupting chemicals (EDCs). Such EDCs are also regarded as endocrine-modulators or endocrine disruptors and are ubiquitous in nature and make their way passively into human body through skin, water-intake, inhalation, and digestion as the humans are always exposed to their multiple sources in routine daily life [2]. Broadly speaking, the list of EDCs includes but not limited to environmental toxicants, pesticides, herbicides, and pharmaceuticals (Fig. 21.1). These EDCs impair the normal functions of hormones and the adverse effects are observed in the form of neurological disorders, sexual abnormalities in both genders, psychological and behavioral issues. They also cause metabolic disorders leading to obesity and type 2 diabetes [3, 4]. The pharmaceutical products happen to act as EDCs (Fig. 21.2) in at least two different ways:

- The pharmaceutical wastes discharged directly from pharmaceutical industry find their way into human body and act as EDCs by interacting with normal functions of the endocrine system in healthy subjects.
- The pharmaceutical products used as medication come across non-target interactions with the endocrine system, thus impair the normal physiological functions.

The regulation of blood glucose level is one of the prime health parameters in humans established through the glucose homeostasis by the adequate production and action of insulin. It suppresses the glucose production and lipolysis to maintain the blood sugar level. It accelerates the energy production or helps to store the extra glucose in muscles, adipose tissues, and liver in the form of triglycerides or glycogen. The elevated glucose level in serum excites pancreatic β-cells to produce insulin [5]. However, amino acids, ketone bodies, and free fatty acids also influence the insulin production. In fact, they alter the cationic flux around the Ca^{+2}/K^{+}

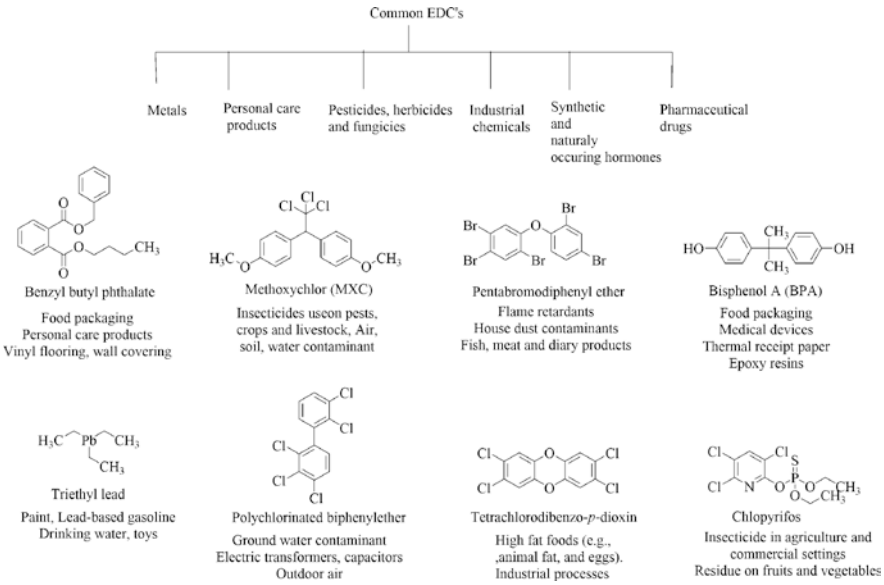

Fig. 21.1 Common endocrine disrupting chemicals.

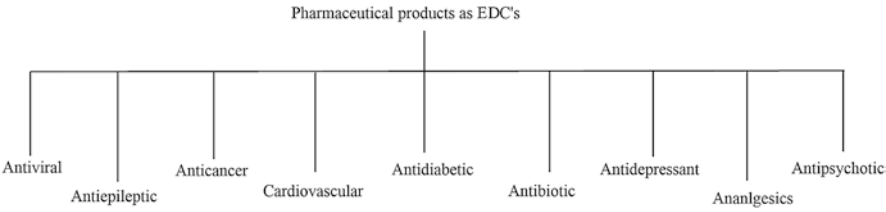

Fig. 21.2 Pharmaceutical products as endocrine disrupting chemicals.

channels in β-cell membranes, thus result in insulin secretion. The impaired glucose metabolism, hampered intracellular transportation, reduced blood flow, and receptor down-regulation cause insulin resistance. The hyperglycemic conditions result in insulin resistance. The alteration in glucose and lipid metabolism due to medications results in weight gain or T2DM [6, 7].

Medications for Immunosuppression as EDCs

The chances of post-transplant organ rejections are minimized by employing immunosuppression drugs like tacrolimus and cyclosporine. Such immunosuppressive agents cause insulin resistance and put adverse effects on β-cells, thus could lead to

hyperglycemic conditions. The subjects receiving tacrolimus have been found to show high tendency of T2D, glucose intolerance, and hyperglycemia; however, the mechanistic understandings are not well elucidated [8, 9].

The glucocorticoids being structurally similar to cortisol (endogenous hormone) manifest immunosuppressant activity by binding to glucocorticoid receptors. Actually, they regulate protein, fat, and carbohydrate metabolisms. They also exhibit endocrinal disturbances and metabolic disorders by interacting with off-target endocrine system. They could cause insulin resistance with impairing of glucose uptake, suppression of insulin secretion or hepatic gluconeogenesis in dose-dependent manner. They enhance production of glucose by stimulating the activities of 11-β-hydroxysteroid-dehydrogenase-1 [10, 11].

In hypothalamus, the glucocorticoids produce effects on the activities of AMP-activated protein kinase and stimulate the intake of fats. In fact, they activate endocannabinoid system which increases fat accumulation in the liver and reduces the energy requirements, thus regulate diet intake. The glucocorticoids could cause weight gain and insulin resistance by stimulating cannabinoid 1 receptor [12]. Almost 20% of the subjects have shown around 10 kg increase in weight during the first year of glucocorticoids administration [13].

Antiviral Medications as EDCs

The antiviral drugs mainly include protease inhibitors which prevent HIV replications by binding to viral-proteases, thus block proteolytic cleavage of protein-precursors and consequently it halts the process of formation of new viral particles. As a side effect, the PIs effects the stimulation of insulin and fat storage as lipodystrophy (Fig. 21.3) [14, 15].

Endocrinologic Agents as EDCs

Oral Contraceptives

The oral contraceptives are structural mimics of ovarian hormones inhibiting the secretion of gonadotropin-releasing hormone from hypothalamus and result in non-stimulation of monthly ovulation. The oral contraceptives are the combination formulation of progestin and estrogen; these hormonal components show little effects on insulin resistance and glucose tolerance but metabolism of lipoproteins is disturbed greatly in a dose-dependent manner (Fig. 21.4). The progestins account for decrease of HDL-cholesterol and increase of LDL-cholesterol in serum while the opposite is observed for estrogen. The estrogen component also increases the triglyceride contents in serum [16–18].

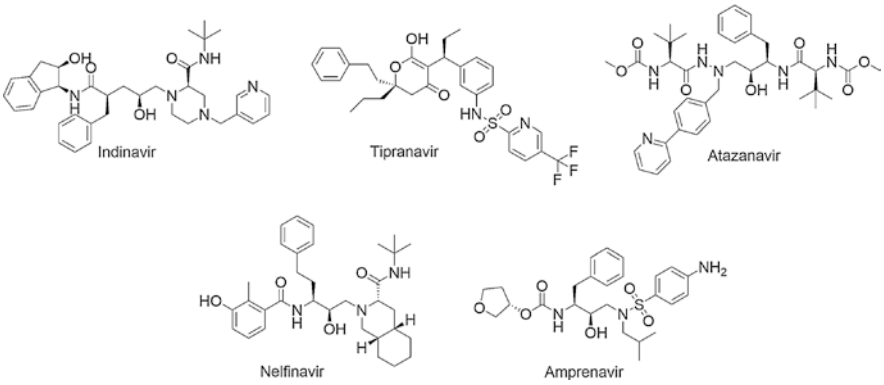

Fig. 21.3 Some commonly used antivirals (protease inhibitors)

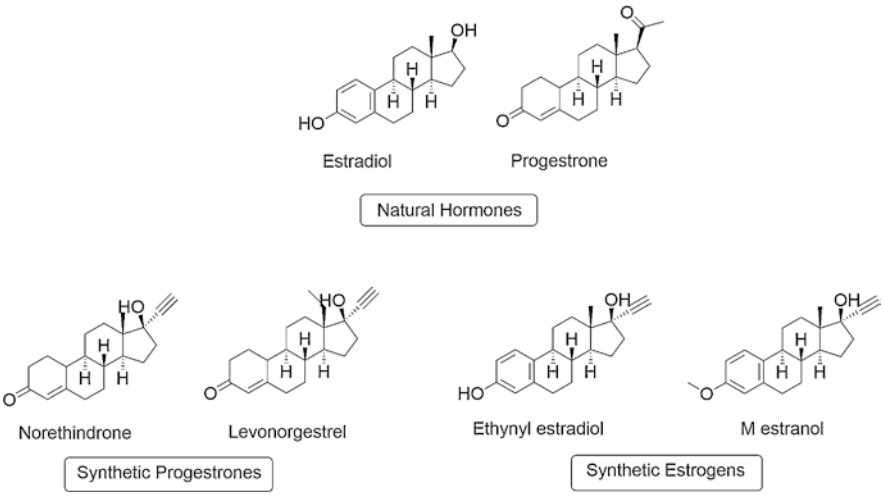

Fig. 21.4 Formulation of oral contraceptives

Medications for Neurologic and Psychiatric Issues

Depression Related Medications as EDCs

The depression related drugs like monoamine oxidase inhibitor and amitriptyline; the less frequently used tricyclic antidepressant shows association with weight gain. However, nefazodone and bupropion; the atypical antidepressants have not shown considerable association with weight gain. The weight gaining capacity of antidepressant receiving subjects has mainly been related to their physiological conditions [19, 20].

Epileptic Disorders and Related Medications as EDCs

The diabetic neuropathy, migraines, and bipolar disorders, etc., are treated mainly using antiepileptic medications. The use of topiramate, valpronate, and gabapentin has been found to associate with the metabolic disorders. The low resting metabolic rate of valpronate along with its long-term usage causes obesity and weight gain. The high doses of gabapentin have also been expected to induce obesity but the effects are less than the valpronate [21, 22].

Medications for Psychotic Disorders as EDCs

Both the first and second generation (atypical) antipsychotic medications are used for the treatment of bipolar, depression, and schizophrenic patients. They have widely been used to treat development disorders. However, the usage of first generation has lost its worth with the passage of time due to cognitive impairments, obesity, and weight gain issues. The underlying mechanistic steps for the induction of metabolic disorders and weight gain by the antipsychotic medications are not well known. The antipsychotic drugs like aripiprazole, ziprasidone, and risperidone cause a little weight gain while olanzapine and clozapine treatments induce obesity considerably [23]. The subjects receiving psychotic medications are prone to diabetes and obesity about two times than healthy ones. The body weight is regulated by the activities at histamine-H, dopamine, norepinephrine, and serotonin receptors. The antipsychotics with more affinities with histamine-H_1 have shown association with weight gain which may be related to insulin secretions [24]. Further, it has been observed that the patients receiving atypical antipsychotic medications are susceptible to hyperlipidemia in addition to glucose metabolic disorders and obesity, thus leading to cardiovascular risks [25, 26].

Medications for Hypertension as EDCs

The subjects suffering from hypertension and cardiovascular diseases generally receive β-blockers or diuretic agents as medications. Both of these antihypertensive agents cause disturbance in lipid metabolism and also induce glucose intolerance [27].

β-Blockers as Antihypertensive Agents

The β-blockers reduce the blood pressure by blocking adrenaline hormone. An increase in triglycerides and decrease in HDL-cholesterol have been found associated with the usage of β_1-selective and non-selective β-blockers. Further, the impair-

ment of lipid and carbohydrate metabolism and insulin sensitivity are the common side effects of most β-blockers especially of the first generation. However, the nebivolol and carvedilol; the third generation vasodilating β-blockers have shown better metabolic profiles and are predominantly preferred for patients of hypertension with metabolic syndrome [28–30]. The side effects of β-blockers appear due to disturbance in insulin secretion and impaired activities of lipid metabolizing enzymes.

Some of the β-blockers cause abdominal fat deposition due to abnormal lipid and carbohydrate metabolism. The adrenergic stimulation cause β-blockade which lead to inhibition of lipolysis resultantly a condition of fatigue appears in patients under β-blocker therapy. The β-receptor antagonist treatments reduce the metabolic rate and energy consumption, thus cause weight gain [31].

Diuretics as Antihypertensive Agents

The diuretics promote diuresis by inhibiting the reabsorption of Na in renal tubular system, thus cause an increased water excretion. The loop diuretics inhibit the reabsorption of about 25% Na by inhibiting the Na-K-Cl cotransporter proteins and increase the urination. Such diuretics also induce the production of prostaglandins to increase renal blood flow [32]. The thiazide diuretics also inhibit the Na reabsorption by blocking Na-K-Cl cotransporter in distal tubules. These diuretics reduce blood volume and arterial pressure and activate the renin–angiotensin–aldosterone system [33]. These diuretics usually cause glucose intolerance and hyperglycemia due to their hypokalemia effect which reduces cardiac output, extracellular fluid volume, and inhibition of insulin secretion. Further, the peripheral utilization of glucose decreases due to the increase of catecholamines. The thiazide diuretics also disturb the lipid and glucose metabolism mainly due to the effects of hypokalemia [34, 35]. Therefore, they are preferred for the patients of type 2 diabetes mellitus and obesity as they cause dyslipidemia and insulin resistance in a dose-dependent manner.

Conclusions

As we know the endocrine system with its hormone producing endocrine glands and their receptors regulate a variety of essential physiological functions in human body. The hormones, the chemical messengers which are secreted directly into circulatory system regulate body's growth and development, embryonic development, and primary sex characters, etc. The endocrine system also regulates glucose and lipid metabolism, very crucial biological functions for the survival of life. However, exogenous chemicals in the form of EDCs could interfere with the normal functioning of the endocrine system. They disrupt the hormonal-production, transportation

process and their physiological actions. Unluckily, human body is always exposed to such EDCs which are ubiquitous in nature and move passively into human body through various unavoidable routes. Among various known EDCs, the pharmaceuticals products could disrupt the endocrine system once they are discharged from pharmaceutical industries or when they are used as medication to cure specific disease but they show non-selective off-target interaction with the endocrine system. So these treatment–drugs become EDCs for those who are already patients and worsen their conditions by impairing lipid and glucose metabolism causing insulin resistance, weight gain, and obesity.

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Chapter 22
Parabens as Endocrine Disrupting Chemicals and Their Association with Metabolic Disorders

Kamran Haider, Kanwal Rehman, Anam Sabbir, and Muhammad Sajid Hamid Akash

Abstract Parabens are used as preservatives to prolong the shelf-life of various products mainly including food products, cosmetics as well as pharmaceuticals. Specific attributes like low cost, diminished toxicity, and high efficacy make them more appropriate for usage and currently being used worldwide. Alternatively, easily absorption by human body and ultimate systemic exposure necessitates their safety profiles. In this chapter, we discussed some undesirable consequences associated with paraben exposure and mainly target their endocrine disrupting potential. Disturbance in endocrine homeostasis provokes as well as worsens metabolic disorder such as thyroid gland dysfunction, obesity, irregularity in sex hormones such as testosterone and estrogen. In addition to this, we have also discussed major sources of paraben exposure (Food, Cosmetics, Pharmaceuticals) and their metabolism in human body.

Keywords Exposure of parabens · Cosmetics · Metabolism of parabens · Pharmaceuticals

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Introduction

Parabens are frequently used as preservatives in food, cosmetics, and pharmaceutical industries over the last 70 years. The reason for their widespread use is their preservative along with anti-microbial effects, which was first reported in 1924. Other features like less toxicity, chemically inertness, and low cost make them more appropriate for their corresponding use [1]. As the humans are continuously exposed to food products, cosmetics as well as pharmaceutical products, their continuously exposure further necessitates safety profiles. Parabens are quickly absorbed through skin and gut, although most are excreted in the urine but still some remain in body, and are associated with several health hazards [2].

The use of parabens in food products is from ancient times, since these inhibit the microbial growth and prevent food from spoilage. Their usage is pivotal especially during the food transportation. This is the reason that each food product has some preservative, otherwise food cannot survive longer [3]. Due to their presence in all foodstuffs and ultimate exposure, their safety and toxicity analysis has become essential for ensuring healthy status. For this reason, different analytical methods are used for safety evaluation. Additionally, various legislation agencies have also fixed regulations for paraben's presence in food products [4]. Furthermore, cosmetic preparations are also widely used by people without any distinction of gender, age, and race. Their use is increasing day by day, and also used for longer period of time. These products also contain parabens because of their preservative action, to make them more viable and enhance their efficacy. Subsequently, parabens free products are demanded and preferred, for safeguarding undesirable consequences on human health [5]. Whenever parabens are exposed to body either by topical application as in case of cosmetics or by oral intake as in case of oral medication. These parabens enter into systemic circulation. The presence of parabens in systemic circulation was confirmed upon paraben exposure [6, 7]. Nevertheless, parabens undergo rapid metabolism and metabolized into mainly Para-hydroxybenzoic acid (PHBA) in the liver and also in the skin. These reactions are catalyzed by estrases, and ultimately parabens are excreted via urine. Parabens are primarily excreted as glucuronide conjugates glycine as well as sulfate [8, 9]. Interestingly, parabens present in topical applications probably have more contribution towards the systemic paraben concentration in comparison to oral intake. This is due to presystemic metabolism of orally intake parabens which usually limits the systemic exposure as seen in in vivo studies [10]. This suggests that primary exposure of humans to parabens is through widespread use of personnel care products [11]. Consequently, parabens are used for their preservative efficacy but associated drawbacks particularly endocrine disrupting effect have limited their usage, irrespective of their favorable properties. Ultimately, use of parabens is being replaced by other compounds to avoid undesirable effects [12].

Major Sources of Parabens

In addition to food products and cosmetics, pharmaceutical products are also potential source for parabens (Fig. 22.1). Since, these are not present as active ingredient but are included in excipients (inactive ingredients), being present in solid dosage form and parenteral as well as topical preparations owing to their anti-microbial and preservative action [13].

Food

Presence of parabens in food samples was evaluated in China on food samples, 282 food samples were collected which was categorized into 13 groups, including cereals, dairy products, meat, eggs, and fruits. The results demonstrated that almost all the food products (detection rate 99%) contain some amount of parabens [14]. Accordingly, these parabens are also considered to have hepatotoxic effect, studies have indicated that co-administration of aqueous extract of ginger protects from parabens induced hepatotoxic effect, and rises anti-inflammatory activity of several enzymes [15].

Also, analysis has revealed that vegetables (109 ng/g) are rich source of parabens, followed by condiments (75.4 ng/g) and then cereals (25.2 ng/g). In addition to this, methyl paraben, ethyl paraben as well as propyl paraben are present in relatively higher concentrations in all foodstuffs [14]. The use of parabens in foodstuffs is continuously increasing including processed vegetables, fats and oils, soft drinks, pickles, and frozen dairy products at a concentration of 450–2000 ppm. Among parabens, methyl parabens along with propyl parabens are most widely used in food stuffs [16].

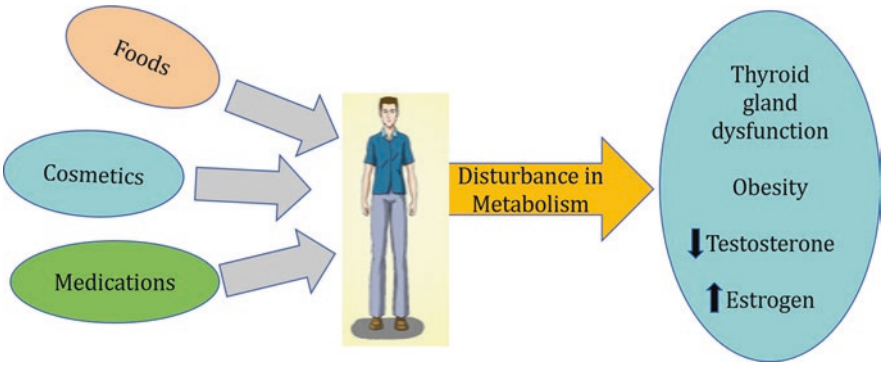

Fig. 22.1 Major sources of parabens and their ultimate undesirable effects. Medications, food products and cosmetics are the major sources of paraben exposure andwlead towards metabolic disturbance such as thyroid gland dysfunction, obesity and disturbance in sex hormones

Cosmetics

Personal care products are also among the major contributor of paraben's exposure. Studies have demonstrated the level of parabens is relatively higher in persons using cosmetics products regularly as compared to non-users. Remarkably, one study has shown 20 times increase in propyl paraben in urine samples of girls who wear makeup on daily basis in comparison to non-user girls [17]. Correspondingly, use of face and hand creams along with hair products and deodorants are interlinked with relatively higher concentration of parabens in urine [18, 19]. Also, one cohort study on pregnant women demonstrated higher level of parabens in urinary samples, because they utilize hair gel, nail polish, lotions, and cosmetics in last 24 hours in comparison to those women who are not utilizing such products [20]. The allowable concentration of parabens regulated by FDA in cosmetic products are 0.4% for single ester and 0.8% for mixture of parabens.

Pharmaceuticals/Medications

Pharmaceuticals have also significant contribution in daily exposure of parabens. Average daily exposure to parabens is estimated to be 76 mg, from which medication contribution is 25 mg, 50 mg from cosmetics and 1 mg from food products. The presence of parabens in pharmaceutical products is due to wide spectrum activity against bacteria, yeast, and molds [21]. Similarly, studies have depicted that medications that contain parabens are also associated with elevated urinary paraben concentration even within hours of usage [13].

Although, these parabens possess low degree of systemic toxicity and generally stable under physiological conditions, recent studies also clarify that repeated applications of topical products containing methyl paraben give rise to the accumulation in stratum corneum of skin. Also, in pregnant women, parabens are interlinked with biomarkers of oxidative DNA damage [21]. Among parabens, methyl parabens have approved 0.15% in oral solution, while maximum potency of 1.8 mg in the tablet formulation. Likewise, propylparaben has been approved up to 10% in oral solution, while high potency of 0.22 mg in sustained action tablet formulation. In the same manner, butyl paraben up to 0.016% in oral solution, while maximum potency of 0.04 mg in sustained action tablet formulation [13].

Metabolism

Evidences have suggested that parabens get absorbed either through inhalation or dietary intake and also upon dermal applications. These undergo metabolism in living organisms [22, 23]. Methyl paraben treated HaCaT keratinocytes significantly

shown elevated nitric oxide production, cell death, lipid peroxidation, oxidative stress as well as activation of transcription factors upon UVB exposure. This suggests that methyl paraben is generally considered as safe preservative in the cosmetics, but may give rise to undesirable effects to human skin upon sunlight exposure [24]. This also illustrates that sunlight may potentiates the harmful effects of parabens especially methyl paraben [24].

Upon hydrolysis, parabens undergo biotransformation process and converted into para-hydroxybenzoic acid along with alcohol in in vivo conditions. Esterases comprising carboxylesterases catalyzes this process [25]. Humans as well as animal studies have depicted that ester bond hydrolysis happens in small intestine and liver microsomes. Although, increase in the length of alkyl chain usually diminishes the process of hydrolysis in the human liver microsomes [26, 27]. Parabens are eliminated from the body mainly through the urine. Alternatively, some number of parabens are also eliminated via feces and bile. This is also advantageous in a way that urinary metabolites are used as biomarker for evaluating paraben exposure to body [22, 28].

Correspondingly, studies have suggested that some parabens especially of low molecular weight or short alkyl chain excreted in unmetabolized form in the urine [29]. For this reason, level of parabens in the urinary sample of 60 Danish men was determined. Concentrations of 98%, 80%, 98% as well as 83% were measured in urine samples involving methyl paraben, ethyl paraben, propyl paraben along with butyl paraben, respectively [30].

Parabens as Endocrine Disrupting Chemicals

Influence on Thyroid Gland

Thyroidhormone has crucial role in normal development along with regulation of metabolism in adults. This hormone has association with body weight as well as energy expenditure. Likewise, hyperthyroidism elevates resting energy expenditure and leads to weight loss. Conversely, hypothyroidism promotes reduced energy expenditure and hence give rise to increased weight [31, 32]. So, thyroid hormone has pivotal role in the cellular metabolism and participates in variety of pathways which are involved in metabolism of lipids, proteins, and carbohydrates. Besides, thyroid hormone is a primary regulator of mitochondrial respiration as well as biogenesis. Patients with abnormality in thyroid hormones mostly develops symptoms of metabolic dysfunction, also having association with cancer [33, 34].

Significant decrease in T4 level is observed upon paraben's exposure in an animal study in prepubertal female rats [35]. One study on adult females also demonstrated decrease in T3 and T4 on butyl paraben exposure, and this decrease was different among racial/ ethnic groups. Some rodent studies also illustrated decrease in thyroid hormone level upon paraben exposure [36]. Thyroid stimulating hormone

(TSH) has a vital importance for regulating thyroid hormone release along with growth of thyroid gland, secreted from anterior pituitary. It stimulates thyroid follicular cells to release T3 (20%), T4 (80%) and thyroxine [37].

Evidence has also suggested altered thyroid hormone levels upon paraben exposure during pregnancy [38]. The balance of thyroid hormone during pregnancy is essential because fetus depends on maternal thyroid hormones, required for fetal brain differentiation and neuronal development. So, deficiency of this hormone can lead to neurodevelopmental problems [39–41]. So, cosmetic products (major source of paraben exposure) should be principally avoided during pregnancy.

In addition to this, hyperthyroidism along with hypothyroidism give rise to insulin resistance, a potential hallmark of metabolic syndromes. Additionally, altered thyroid hormones are also associated with diabetes mellitus, dislipoproteinemia, arterial hypertension, and changes in body weight [42]. Although results of paraben exposure and disturbance in thyroid hormone levels are more prominent in animal studies, further human studies associating parabens and thyroid hormone levels are required to confirm potential findings of animal studies [36].

Influence of Parabens on Testosterone

Testosterone is a primary hormone essential for the developmental growth and participates pivotal role in maintaining male phenotype throughout the life. Unlike to women, where estrogen level decline suddenly during menopause, testosterone level in men decreases gradually with aging [43]. Exposure of parabens is interlinked with diminished testosterone in experimental studies on rats, also adversely affects male reproductive functions. Propyl treated rats also demonstrated significant decrease in daily sperm production [44]. Likewise, paraben's exposure has illustrated undesirable effects in animals, yet human epidemiologic studies are lacking. Although one epidemiologic study presented no relationship between hormonal level and urinary parabens, yet modest sample size and intraindividual variability in exposure have limited to confirm any suitable results [45].

Biochemical evidences demonstrate the involvement of testosterone in enhancing glucose utilization by promoting glucose uptake, mitochondrial oxidative phosphorylation and glycolysis. Additionally, testosterone also mediates role in lipid homeostasis in insulin responsive target tissues like skeletal muscles, liver, and adipose tissues [46]. Accordingly, testosterone also possesses defensive action on pancreatic β-cells [47]. Ultimately, low testosterone level accelerates the risks for insulin resistance and evidently give rise to diabetes. Also, low level of testosterone is observed in insulin resistant patients [48, 49]. Consequently, low testosterone levels (either due to paraben exposure or other reason) are interlinked with raised insulin resistance, impaired mitochondrial function, increased triglyceride levels, diminished HDL cholesterol and also give rise to five-times increase in risks for cardiovascular diseases [50–52].

Likewise, one study has also elucidated decrease in serum testosterone concentration I dose-dependent manner in 3-weeks old rats. Surely, remarkable decrease was observed in group receiving the maximum dose of propyl paraben [44]. Therefore, keeping in view the aforementioned complications associated with paraben usage, their use should be minimized or entirely restricted notably in persons who have diabetes (as low testosterone level in diabetic patients).

Parabens and Obesity

Obesity has becoming a vexing problem in both, developing and developed countries. It is abnormal or elevated fat accumulation interlinked with many metabolic disorders in the body [41]. Actually, luxurious life style as well as environmental factors along with genetic predisposition have pivotal role in provoking obesity [53]. Definitely, obesity diminishes quality of life along with life-expectancy due to its association with metabolic syndromes such as hypertension, osteoarthritis, sleep apnea, type 2 diabetes, fatty liver disease, and myocardial infraction [54].

Evidence has suggested that parabens contribute in adipogenesis. Thus, giving rise to obesity [55]. Additionally, exposure of endocrine disrupting chemicals (EDC) during early life is considered potential hallmark for childhood as well as adult obesity [56]. For this reason, parabens mediated endocrine disrupting effect is mainly responsible of their undesirable effects, irrespective of their less toxicity [57]. Evidence has suggested that parabens promotes adipose differentiation [55, 58]. As illustrated that adipocytes form during early life and usually their number does not rise in lean adults. Yet, precursors cells may be differentiated to adipocytes in adults owing to increased demand for energy storage [59]. Subsequently, parabens mediated differentiated would add up this process and promotes obesity epidemic in exposed population. Parabens are thought to mediate their effect through peroxisome proliferator-activated receptor gamma (PPARγ) along with the glucocorticoids receptors (GR) [60, 61].

The contribution of parabens in obesity in in-vivo studies is under major consideration. One study in 27 healthy women has demonstrated positive association of parabens with plasma adipsin levels (secreted by adipocytes into bloodstream). When blood samples were collected during their menstrual cycle, their results depicted elevated methyl paraben along with propyl paraben in women with BMI 25–34.9 as compared to women with BMI 18.5–24.9 [62]. Despite many evidence, contribution of parabens in obesity/adipogenesis in in vivo studies and underlying molecular mechanism needs further consideration and evaluation [55]. Additionally, exposure of endocrine disrupting chemicals (EDC) during early life is considered potential hallmark for childhood as well as adult obesity [56]. For this reason, despite less toxicity of parabens, their participation as an endocrine disrupting chemical is mainly responsible for their undesirable effects [57]. Evidences have reported that parabens promote adipocyte differentiation [55, 57]. Given the above, parabens use must be avoided and more particularly in persons who are obese or

overweight, otherwise these may lead to numerous metabolic disorders mainly including insulin resistance. Thus, increasing morbidity and mortality rates. So, it is advisable to minimize the usage of parabens.

Influence of Parabens on Estrogen

Estrogen is an important steroid sex hormone, associated with various functions including cholesterol mobilization, cardiovascular system functions, skin physiology, regulating bone density, and brain functions [63]. In females, estrogen is mainly responsible for regulating secondary sexual characteristics as well as development of reproductive tissues at puberty [64]. Estrogen mainly mediate their effect/functions through their receptors α and β (ERα and ERβ) [63]. The 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1) as well as 17β-hydroxysteroid dehydrogenase type 2 (17β-HSD2) maintain local balance among potent and weakly active estrogens. 17β-HSD1 catalyzes the conversion of weak active estrogen (E1) into the potent estrogen estradiol (E2) as shown in Fig. 22.2. Conversely, 17β-HSD2 performs the opposite function and hence leading towards diminished concentration of active estrogen (E2) [65].

Undoubtedly, all the substances which inhibit 17β-HSD1 leads towards anti-estrogenic characteristics and hence decreases local active estrogen concentration [66]. Studies have shown that parabens inhibit 17β-HSD2. More specifically, larger parabens also size dependently inhibit 17β-HSD1 activity. Also, Para-hydroxybenzoic acid (PHBA) which is primary metabolite of parabens also possesses slight estrogenic properties. Thus, all suggesting that parabens mediate estrogenic effect and

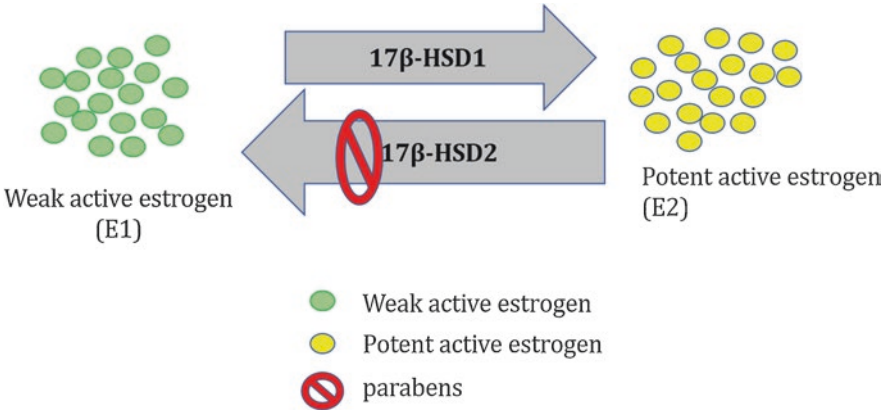

Fig. 22.2 Inadequate active estrogen (E1) is converted into potent estrogen estradiol(E2) by 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1). Similarly, 17β-hydroxysteroid dehydrogenase type 2 (17β-HSD2) catalyzes the back conversion into weakly active estrogen (E1). Evidence has suggested that parabens inhibit 17β-HSD2, thus possessing estrogenic behavior

interfere with normal estrogen level [67]. In addition to this, estrogenic effect of parabens (methyl-, ethyl-, propyl-, and butyl-) was reported in the estrogen dependent human breast cancer cell line MCF7 [68]. Finally, we can summarize that paraben's use should be minimized in women specially to avert breast cancer risks. This can be done by no or minimum use of cosmetics, safeguarding their breast cancer risks as well as other consequences due to estrogenic effects.

Conclusion and Future Prospective

The aforementioned convincingly studies suggest that parabens are being largely used in cosmetics, medications and also food products owing to their preservative activity and relatively less toxicity. Undoubtedly, their presence imparts particular attributes to products and they can relatively be stored for longer period of time. But unfortunately, despite their suitable characteristics, these also possesses some undesirable effects on human health. Their major harmful effect on human body is their endocrine disrupting potential, which interfere with numerous physiological endocrine functions. Ultimately, leading towards many metabolic disorders.

The major endocrine disrupting effects which are consequences of paraben's exposure include thyroid gland dysfunction, leading towards hyperthyroidism or hypothyroidism. This problem is more troublesome for fetus during pregnancy. The reason is that fetus depends upon maternal thyroid hormone, any disturbance in maternal thyroid gland functioning during pregnancy give rise to defects in fetal neuronal development as well as brain differentiation. Furthermore, paraben exposure is associated with decrease in testosterone level in males. Further, this diminished testosterone level is interlinked with various abnormalities in reproductive system, insulin resistance, and cardiovascular problems. In addition to this, parabens also promote adipocytes differentiation and increase obesity epidemic in the exposed population. Also, parabens possess estrogenic effects. Generally, females are more prone to all undesirable effects owing to parabens. The reason is as more cosmetic products are utilized by females in comparison to males. Additionally, paraben's exposure by topical products is more harmful as compared to oral route, as oral route limits systemic exposure of parabens by pre-systemic elimination process, causing less undesirable effects. Likewise, parabens evidently worsen the predisposing factors for metabolic disorders such as insulin resistance, disturbance in thyroid gland functions, impairment in sex hormones, cardiovascular problems as well as obesity.

Although, certain paraben mediated effects are more commonly and easily observed in animals, yet human studies are lacking. Hence, well-designed human studies should be conducted and evaluated to estimate consequences in human body rather than in animals. Keeping in view all above mentioned aspects, we can summarize that these should be used within the ranges as described by FDA and it is also necessary to minimize their usage or these may be replaced by other substances with less or no undesirable effects.

Conflict of Interest Nothing to declare.

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Chapter 23
Role of Aflatoxins as EDCs in Metabolic Disorders

Shakila Sabir, Kanwal Rehman, Fareeha Fiayyaz, Shagufta Kamal, and Muhammad Sajid Hamid Akash

Abstract Aflatoxins (AFs) producing fungi (*Aspergillus* species) are extensively spread in the environment and widely contaminate the human and animal feed. AF has been recognized as substituted bisfuranocoumarins, a secondary fungal metabolite. It has been recognized that AFs may cause hepatotoxicity, mutagenicity, nephrotoxicity, genotoxicity, teratogenicity, and immunotoxicity. Therefore, the International Agency for Research on Cancer has categorized AFs as class I human carcinogen. AF undergoes phase-I and phase-II metabolism in the liver. AFs-mediated cell damage may be due to the production of free radicals. The key mechanism behind AF-induced toxicity is the induction of oxidative stress. AF potentiates inflammatory responses. Additionally, AFs are also found to be involved in impaired lipid and carbohydrate metabolism. Although, attention has not been given to AFs-induced metabolic disorders, metabolic abnormalities produced by AFs clearly indicate that AFs may increase the susceptibility to develop metabolic disorders.

Keywords Lipid metabolism · Carbohydrate metabolism · Oxidative stress · Aflatoxin metabolism

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Introduction

Mycotoxins are produced from various species of fungi. They are commonly found in many food items. Mycotoxins may exist in any stage of food products including production, processing, and preservation. Owing to the chemical stability, they may persist long-lasting even after the eradication of fungi [1]. Aflatoxins (AFs) are considered as most frequently found mycotoxins in food products. Primarily, researchers isolated this toxin from *Aspergillus flavus* that is why it is called as aflatoxin ("a" was taken from *Aspergillus* and "fla" from the word flavus). There are almost 20 AFs intermediates produced from *Aspergillus* species [1, 2]. Chemically, AFs belong to furanocoumarins family. They have two basic structures difurocoumarocyclopentenone (such as aflatoxicol, AFB1, AFB2, AFB2A, AFM1, AFM2, and AFM2A) and difurocoumarolactone (such as AFGM1, AFGM2, AFGM2A, AFB3, AFG1, AFG2, and AFG2A). AFs are called as AFB and AFG due to blue and green fluorescent light emitted, respectively, under UV light during thin-layer chromatography. However, numbers 1 and 2 denote major and minor compounds, respectively [3, 4].

AFs contamination is majorly found in the cereal-based products including maize, rice, sorghum, dried cassava, millet, groundnuts. It may also be found in other kinds of food items owing to poor processing or storage conditions. Additionally, it may also be found in animal products like milk or eggs due to contaminated feed provided to the animals [1, 5]. Trout, ducklings, rats, cattle, swine, and poultry are a few examples of the animals that are sensitive for AFs-contaminated feed [5]. AFs are regarded as a naturally found food-borne toxin that is associated with different diseases and massive deaths both in humans and animals. That is why they are of special health concern globally [6]. Among all kinds of AFs, AFB1 is considered as the most hazardous toxin with great potential for mutagenicity and carcinogenicity to humans and livestock. AFB1 has been categorized into group I carcinogen by the International Agency for Research on Cancer [7]. The risk of carcinogenicity induced by AFs depends on various other factors such as hepatitis B infection, age, gender, nutritional status, and concentration of AFs consumed [8, 9]. Additionally, AFs also have the potential for the induction of immunotoxicity in various species [10]. AF may slow down the blastogenic response towards the mitogens, reduce the compliment titers, decrease the macrophage activation, and depress the delayed hypersensitivity response [11].

Aflatoxin Outbreak

In 1974, a massive outbreak of AFs-induced hepatitis happened in Rajasthan and Gujarat, India. This outbreak resulted in almost 106 deaths [12]. This major outbreak remained for two months and it was just retained within tribal areas where people were taking aflatoxin-contaminated maize food. The earliest analysis

revealed that this AFs come from *A. flavus* [12, 13]. During the same year, another AFs outbreak was reported in northwest India that equally affected humans and animals [13, 14]. In 1981, another major AFs outbreak was reported in Kenya [15]. Since 2004, numerous aflatoxicosis outbreaks have been documented by the Centers for Disease Control and Prevention globally, resulted in 500 cases of acute illness and a total of 200 deaths [16, 17]. Many outbreaks have been documented in Kenya in 2004 that was due to maize grown at home. Later on, it was found that this maize was contaminated with molds [16]. In 2013, many European countries (Romania, Croatia, and Serbia) reported the AFs contamination of milk nationwide [18].

Biotransformation of Aflatoxin

Biotransformation of AFs majorly happens in the liver. AFs passes through both phase-I and phase-II type of metabolism. Phase-I metabolism majorly includes oxidation, reduction, and hydrolysis. Phase-I metabolism products serve as reactants for phase-II metabolism, which majorly involves the conjugation reactions. Phase-I metabolism results in either detoxification or activation of a given compound. While phase-II metabolism leads either to detoxification or generation of biochemical lesions. Cytochrome P450 (CYP450) system is majorly involved in phase-I metabolism, while phase-II metabolism includes sulfation, glucuronidation and amino acid, and glutathione conjugation reactions [19].

Phase-I Metabolism of Aflatoxins

CYP450 subfamilies are involved in the oxidation of AFB1 and converted it into several other metabolites. Among all metabolites of AFB1, AFB1 epoxide has been recognized as mutagenic while all others are harmless detoxified products. AFB1epoxide (highly potent metabolite) is an active electrophile and it has a strong affinity with nucleophilic oxygen, nitrogen, and sulfur-like heteroatoms found in cellular constituents [20]. Conversion of AFB1 to AFB1 epoxide is an important reaction that promotes the covalent binding of AF to various cellular macromolecules including protein and DNA. This reaction takes place with the help of CYP1A2 and 3A4 [21]. CYP3A4 may be involved in both activation as well as detoxification of AFB1. CYP3A4 is abundantly found in the liver and small intestine. During the intestinal biotransformation, epoxidation does not enhance the risk of liver cancer. CYP3A4, abundantly found in the liver, is majorly involved in the activation of AFB1. Moreover, CYP1A2 and few other CYP450 enzymes also contribute to its activation to some extent [22, 23]. CYP3A4 mostly forms AFB-2,3-epoxide (genotoxic), while CYP1A2 produces the nongenotoxic endoisomers [22]. CYP1A2 shows a great affinity for activation of AF-B1 at low concentrations after dietary exposure [24]. Some intermediates of the AFB1 pass through some other chemical

reactions in Phase II after binding with GSH to produce the less toxic polar compounds that are directly excreted through bile and urine. However, aflatoxin B1-8,9-epoxide (AFBO) and AFB1-dihydroxide intermediates have carcinogenic properties, while AF-B2 induces acute toxicity, hepatic necrosis, and cellular enzyme inhibition [25].

Phase-II Metabolism

Phase-II reactions leading towards the detoxification include conjugation to GSH, sulfate, and glucuronic acid. The AFB1 metabolites obtained from Phase-I metabolism undergo phase-II enzymatic reactions with the help of glutathione-S-transferases that predominantly catalyze the conjugation reactions. After phase-I oxidation reaction, AFs may be rapidly conjugated with thiol (SH) group (during Phase-II reactions) resulting in detoxification and elimination of toxic products [26, 27].

Mechanism of Toxicity

Aflatoxin-Induced Oxidative Stress

Oxidative stress serves as a key mechanism behind aflatoxicosis. Both AFs and their metabolites may induce oxidative stress. AFB1, a carcinogenic food contaminant, is generally categorized among the most potent hepatocarcinogens in both human and experimental animals. AFB1 metabolism potentiates free radicals production leading to cell damage [19, 24]. AFB1 is metabolized in the liver with the help of CYP450 to AFBO, which binds with protein and DNA and makes the adducts. The hazardous effects of AF generally produce owing to the binding of epoxide derivative with DNA. CYP450 enzymes produce superoxide and hydrogen peroxide as intermediate compounds resulting in some cellular pathological changes and apoptosis [20]. The genotoxicity of AFB1 may be partly owing to the excessive production of ROS like OH, O_2^-, and H_2O_2 during the metabolism of AFB1 by CYP450s in hepatic tissues. ROS may attack various soluble cellular compounds and membranes resulting in impairment of different cellular functions and eventually, cytolysis occurs [28]. It is being reported that free radicals production during AFB1 metabolism followed by the oxidative damage may be one kind of damage induced by AFB1 [21]. Oxidative damage from these ROS may, in turn, induce tissue damage through various mechanisms comprising DNA damage, protein oxidation, lipid peroxidation, and thiol depletion. Studies have shown that AFB1 may alter the cell cycle and trigger the apoptotic-signaling pathways in hepatocytes in vitro [29].

Aflatoxins-Induced Inflammatory Responses

It has been observed that AFB1 decreased the expression of IL-4 expression (anti-inflammatory) but increased the expression of IFN-γ and TNF-α (pro-inflammatory cytokines) form natural killer cells [22]. These findings indicated that AF-B1 exposure potentiated the inflammatory responses by regulating the cytokines related genes expression. Moreover, AFB1 interrupted the process of the antigen-presenting capacity of porcine dendritic cells. It may be a possible mechanism behind AF-B1-induced immunotoxicity [23]. It has also been reported that AFs exposure decreased the efficiency of immunization in children and made them susceptible to infections [30].

Aflatoxins-Induced Lipid Metabolism

The liver is considered as a target organ for AFs toxicity accompanied by dyslipidemia. Dyslipidemia may happen owing to altered expression of lipid and lipoprotein metabolizing genes [26]. Literature has shown that plasma dyslipidemia due to AFB1 exposure was characterized by an elevated level of cholesterol, free fatty acids, and triglyceride with a reduced level of phospholipids and HDL_3–cholesterol. On the other hand, hepatic dyslipidemia after AFB1 exposure was characterized by an elevated level of cholesterol, phospholipids, and triglyceride. Additionally, expression of all 5 lipid-related genes was significantly changed after AF-B1 exposure [27]. In DM, glucose loss due to deficiency of insulin enhances the demand for lipid oxidation for the purpose of energy metabolism and the key mechanism working behind it is β-oxidation of fatty acids [31]. Fatty acids beta-oxidation comprises of multi-steps in which fatty acids are processed to produce acyl-CoA which enter TCA cycle. It has been observed that AFs exposure to diabetic rats significantly reduced the expression of two important fatty acid β-oxidation enzymes named 17 β-hydroxysteroid dehydrogenase-IV and trifunctional enzyme subunit alpha [32]. Another study proved that AFs exposure caused the lipid metabolism disorders in addition to the increased gluconeogenesis in rat liver [26].

Strategies to Control Aflatoxin

It is needed to control AFs exposure at all stages from field to dining table in order to reduce the risk of health hazards. Pre-harvest approaches include practicing targeted plant breeding, improving the host plant resistance, and usage of various biological control methods. Pre-harvesting techniques may be followed by post-harvesting techniques for better control, including appropriate drying, processing, and storage of susceptible crops. It is a rationale to make arrangements for

suitable alternative uses in case of damaged crops. National authorities may help to control AF contamination in various ways such as the removal of contamination sources, introduction to better agricultural techniques, enforcement of strict food safety standards, and to launch the educational campaigns for awareness regarding AFs [33–35].

The various dietary interventions may be adopted to reduce the AFs-induced health hazards. One simple intervention is to reduce the consumption of crops that have more chances of AF contamination like maize and groundnuts. Instead of it, one may consume food items with minimum risk of AFs contamination like pearl millet and sorghum [36]. If it is not possible to quit the food items with higher susceptibility of AF contamination, then it is rational to include AF adsorbent in the meal like zeolites, bentonites, diatomaceous earth, activated charcoal, and plant-based fibers. These adsorbents have varying degree of binding with AFs and reduce AFs bioavailability [37]. Green tea polyphenols are found to be very effective against AFs-induced risk of cancer. Studies have shown that they worked by modulating the metabolism of AFs. A chlorophyll derivative called chlorophyllin is a component of green vegetables has anticarcinogenic properties [38]. Chlorophyllin works against AF as sequestrant and it reduces the absorption of AF from digestive tract. Additionally, chlorophyllin has been identified as enzymes inducer and enhances the detoxification process of AFs [39, 40]. AFs increased the production of ROS and chlorophyllin acts as free radical scavenger [41].

It is evident from the studies that lactic acid bacteria have the potential to bind AFs [42]. Lactic acid bacteria are commonly used for the fermentation of different food items such as fruits, vegetables, and dairy products. Inclusion of fermented food products in meal is considered as a good preventive measure against AFs [41].

Conclusion

AFs have been recognized among major sources of food-related disease outbreaks. Lack of knowledge is a major issue behind the consumption of AFs-contaminated food products. The excessive level of AFs in food in under-developed countries is of major concern. Although there are different forms of AF, AFB1 produces the most hazardous health effects. Toxic effects of AFB1 are due to its active toxic metabolite named as AFB1 epoxide by hepatic CYP450 enzymes. This epoxide may form adducts with certain macromolecules including protein, DNA, and RNA and bring molecular changes at the cellular level.

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Conflict of Interest Author declare that there is no conflict of interest.

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Part III
Treatment Strategies of EDCs-Induced Metabolic Disorders: From Prevention to Intervention

Chapter 24
Hormone Harmony in Metabolic Disorders

Nizwa Itrat

Abstract Hormones act like physiological internet signals for communication among all the human systems and effects immunity, metabolism, and reproduction. Nutritious and balanced food plays an important role in proper production of hormones especially quality of fats. Omega-3 fatty acid is key ingredient for proper hormone production and their normal functions. Nuts, seeds, olive oil, coconut oil, and fatty fish provide healthy amount of omega-3 fatty acids. Cruciferous vegetables and Nutraceutical compounds from fruits like pomegranate, figs and dates maintain and stimulate balance hormonal network in the blood. Probiotics from food help in proper functions of hormones by detoxification of liver and gut. Seeds like flax seed and sesame seeds play important role in female hormonal regulation. A good quality sleep and stress reliving exercises also normalizes the imbalance hormones.

Keywords Balance hormones · Nutrition · Metabolism

Introduction

Every time when a person eats or feels the body response through a specific hormone change. These small chemicals called hormones are like a mystery of body. Because hormones can make the life of person a haven in balance state. But the imbalances of them make that person trouble from mood swing to digestion. Each body system depends on the harmony between these hormones. And imbalance of hormones are little or over production of them resulting in less or excessive metabolic responses in metabolism leading to metabolic diseases [1]. Interruptions of

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patterns of hormonal responses to any stimulus must inevitably lead to consideration of the metabolic effects of the involved hormones. Massive amounts of recent endocrinological data indicate that most hormones have surprisingly broad range of effect on metabolic processes.

The effects of Cortisol, for example, include those on carbohydrate, lipid, protein, sodium, potassium, phosphate, chloride, calcium, magnesium, and water metabolism. It influences processes such as energy production, acid-base balance, growth, wound healing, lactation, and resistance to infection. It affects tissues and organs such as liver, muscle, adipose tissue, brain, kidney, gastrointestinal tract, bone, cartilage, connective tissue, blood cells, lymphoid tissue, skin, and the cardiovascular system. Other hormones including thyroxin, insulin, growth hormone, and epinephrine' similarly have a multiplicity of diverse effects. Insulin has a potent stimulating effect on protein biosynthesis, but it also has a strong effect on carbohydrate metabolism, which would appear to be an undesirable or unnecessary "side-effect" in this instance. Growth hormone, on the other hand, while being synergistic with insulin in its effect on protein metabolism, antagonizes the effect of insulin on carbohydrate metabolism. Concurrent or coordinated elevations of both hormones might then logically be expected to exert a strong, selective effect on protein synthesis with minimal associated effects on carbohydrate metabolism. The adrenal corticosteroids are also known to counteract the effects of insulin on carbohydrate metabolism [1].

The sympathetic adrenomedullary system with the secretion of epinephrine and norepinephrine, and the hypothalamic pituitary adrenocortical (HPA) system with the secretion of cortisol. These hormones have often been used as objective indicators of stress in the individual. However, through their bodily effects, they are also a link between the psychosocial environment and various health outcomes. From a series of studies of women and men, it was concluded that gender roles and psychological factors are more important than biological factors for the sex differences in stress responses [2].

Importance of Healthy Hormones

Body experiences different changes in hormones during different life stages and balancing hormones is not an easy task. The change in single hormone production has effects not only appetite, mood, and metabolism but almost on all others hormones in the body. *The metabolism and health greatly depends on hormones and there optimal production. Hormones have profound impact on mental as well as physical health* [3]. *They control mood, emotional health, appetite, weight, and physical health.* Several natural mechanisms regulate the production of these little body messengers in the normal range and life quality will become better with this harmony [4]. A schematic representation of importance of hormonal balance has been shown in Fig. 24.1.

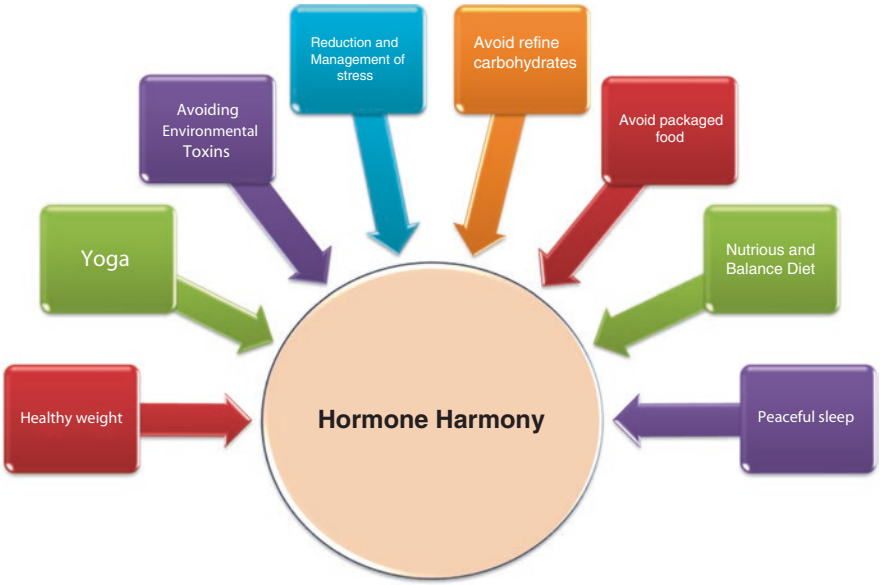

Fig. 24.1 Factors contributing in balance hormone production

Importance of Balance Nutrition for Balance Hormones

The most important factor for normal and precise hormonal production is balance nutrients. The macro- and micro-nutrients in proper combination are important for glands health. These glands use them to produce hormones. The well balanced diet comes with multiple functions for body, mind, and soul; it also creates balance in body by maintaining hormone in normal range. Nutritious diet can even correct imbalance of abnormal or low hormonal production. In the same way some processed foods and refined drinks intake are related to serious health issues. They cause low production or even block the production sites (Fig. 24.2).

Macro-Nutrients and Endocrine Health

Malnutrition attribute to an alteration from an ideal nutrition intake according to the age, gender, and body weight. All macro-nutrients such as proteins, carbohydrates, fats, with micro-nutrients including vitamins and minerals have strong impact of endocrine system. Excessive caloric consumption leads to adiposity. Moreover, this extra caloric intake is also linked with increased risk of insulin resistance and impaired glucose intolerance. The correlation of higher body mass index with increased risk of endocrine diseases can be seen among all age groups. Reducing weight by caloric reduction is helpful for improved function of pancreatic α- and

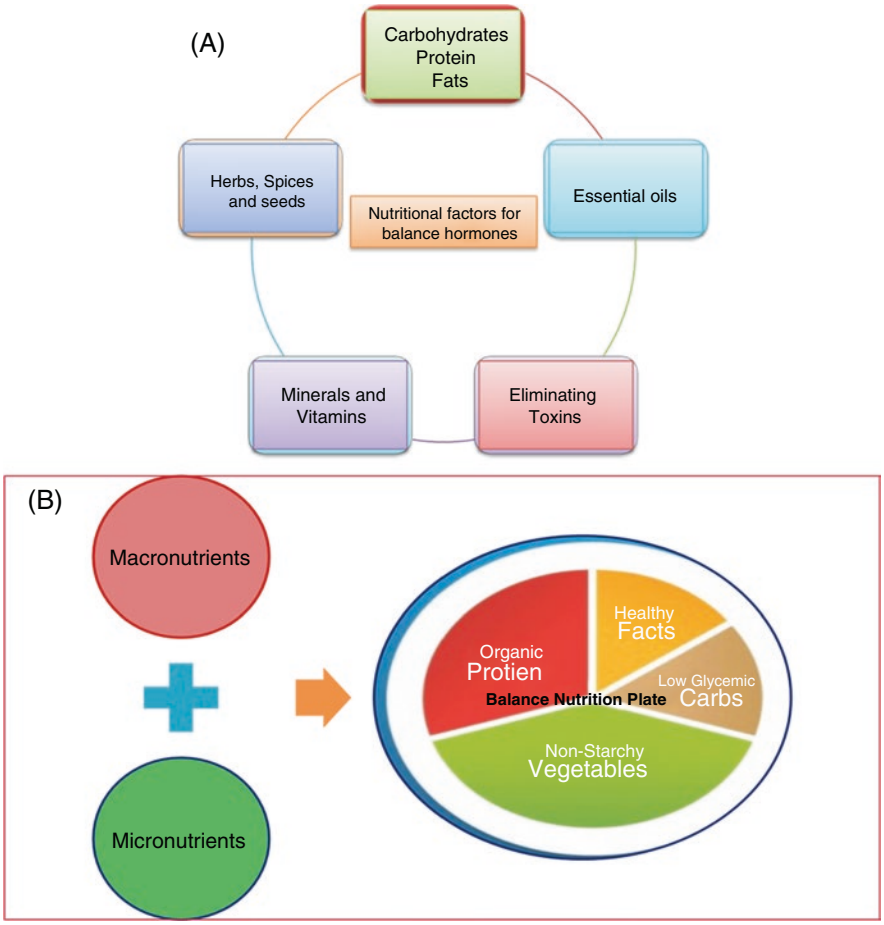

Fig. 24.2 (**a**) Nutritional factors for balance hormonal production and (**b**) balance nutritious plate for hormone harmony

β-cell [5]. Both over nutrition and under nutrition are linked with an increased risk of metabolic syndrome in future [6].

Effect of Carbohydrates on Hormones Production

Carbohydrates are body's chief source of energy. Some sources of CHO are considered as good due to high fiber content. These are complex CHO and in normal quantity they do not have any adverse effects on any hormonal production. But some refine and highly processed simple sugars have adverse effects on insulin production and body's metabolism. Insulin production is highly depended on the

amount and quality of carbohydrate consumed. Actually, insulin is a product in response to high amount of glucose in blood stream. This insulin relates to a series of chemical problems on other hormones [7]. The balance in blood glucose level is the best way of attaining hormonal balance. The best way to maintain balance in Blood sugar can be attained by controlling the type and amount of carbohydrate consumption. Good carbohydrates are complex like whole wheat flour, oats, barley, and brown rice. Fruits with fiber are also loaded with lots of phytonutrients and antioxidants. Green leafy vegetables are loaded with minerals and fiber, are good for thyroid gland functions. Fiber controls blood sugar and normalizes insulin secretions in normal range [3].

Protein for Hormone Production

Eating good quality of protein provides amino acids for hormone production. Insulin and growth hormone production directly depends on protein quality. Animal sources include eggs, chicken, mutton, beef, fish, and Turkey. Plant sources including beans, lentils, seeds, and legumes, are also good for proper hormone production (Fig. 24.3). Some proteins have adaptogenic effect. Lentils and wild trout are good examples of adaptogenic proteins [8].

Fig. 24.3 Dietary sources of proteins

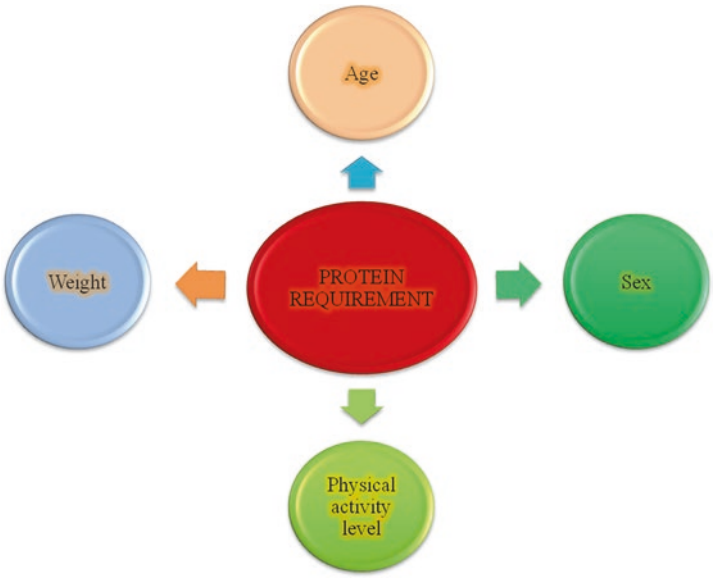

Fig. 24.4 Protein requirement factors

It is important to incorporate Mercury free sea foods for protein source as mercury is endocrine disruptor element for thyroid and estrogen [9]. The protein requirement depends on different factors like gender, age, physical activity, and physiological condition like pregnancy or lactation (Fig. 24.4). Grass fed animal meat, wild fish, organic chicken, and eggs are considered good proteins for endocrine health. Less protein intake has several effects on hormonal production (Fig. 24.5). But some high fat animal proteins can cause inflammation, damage the Gut and over stimulation of endocrine glands resulting in abnormal hormonal production [10].

Essential Fatty Acids for Endocrine Health

Fats and cholesterol are used for making structures of hormones. They are essential for hormone production and function. Healthy dietary fat consumption is important for normalizing and balancing hormones. There are different types and sources of dietary fats (Fig. 24.6). Human body requires essential fatty acids from diet because the body is unable to form them. Brain needs essential fatty acids for its structural formation to maintain healthy nerves and neural connections. Omega 3 fatty acids are important for depression treatment. The dietary sources include canola, flaxseed, walnut, and hemp oils. These oils are rich sources of omega-3, alpha linolenic acid (ALA). Evening primrose oil and hemp seeds are good sources of healthy omega 6 fatty acids. This is important in reducing hormonal imbalance depression

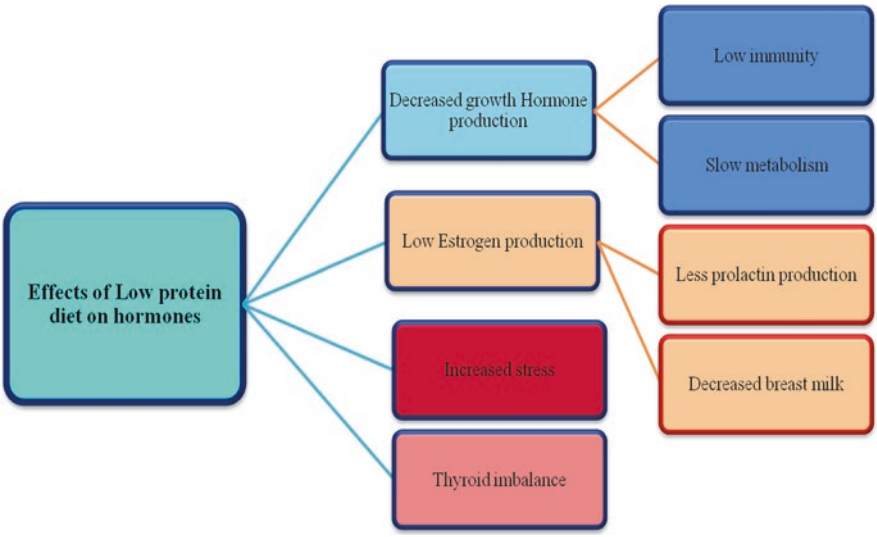

Fig. 24.5 Effect of low dietary protein intake on different hormone production

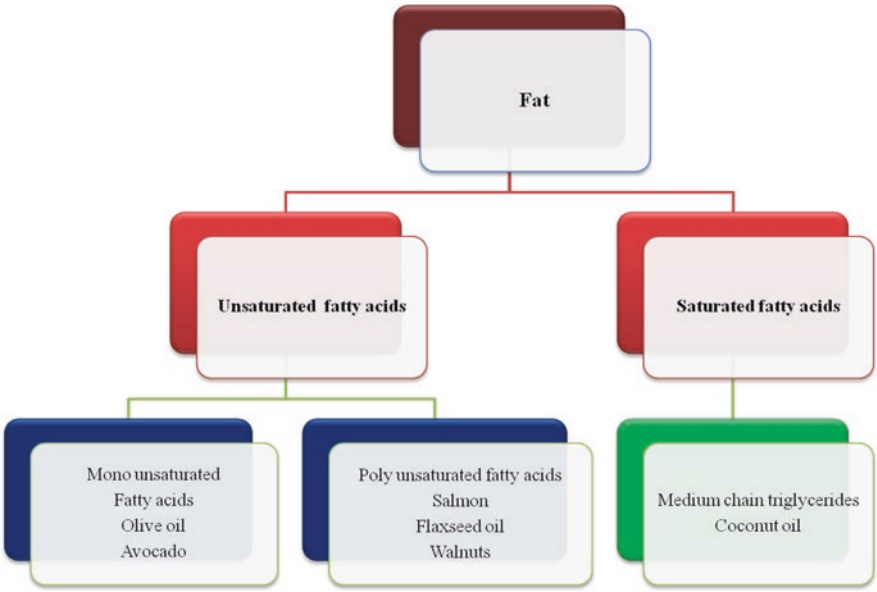

Fig. 24.6 Different types of dietary fat

and stress. Omega 3 fatty acids are more crucial for body especially glands. Woman requires more omega 3 fatty acids than man. Dietary sources of healthy fats include egg yolk, nuts, seeds, Avocado, Flaxseed oil, almond oil, and fish oil [11].

Micro-Nutrients for Balance Hormones

Minerals and vitamins play crucial role in hormone production and proper function because they are structural part of many hormones or involved in stimulation of their production. Iodine is vital for healthy thyroid function and thyroxin production [5, 12]. It is main structural part of T3 and most common but preventable form of hypothyroidism. Iodine deficiency results in cretinism, Goiter, mental retardation among children, and hypothyroidism. Dietary iodine from fish and nuts and supplementary iodine from iodide salt may prevent the adverse effects.

Selenium is an important trace mineral. It works as anti-oxidant and also helpful for thyroid gland function with iodine. Naturally it has four oxidation states elemental selenium, selenide, selenite, and selenate. Mostly biological functions are performed by selenoproteins. These proteins are important in cellular defense against reactive oxygen species [13]. So the less amount of selenium in body will increase the risk of oxidative stress and damage to blood vessels [14].

Magnesium functions as a cofactor for hundreds of enzymes. Low levels are associated with increased BMI and metabolic syndrome. The dietary intake of Mg has protective effects on bone density. Magnesium is more crucial for men's hormonal health. It enhances free testosterone with more health benefits of better moods and peaceful sleep.

Zinc is also important part of all enzymes including catalytic, structural, and regulatory systems. The best role of Zinc in endocrine health is insulin synthesis and regulation. As it acts as anti-oxidant, it is important in immunity and anti-inflammatory responses [15]. Higher absorption of sodium results into increased parathyroid hormone secretion. Calcium, phosphorus, magnesium, and potassium among macro-minerals and boron, copper, zinc, and silicon are important for bone health and hormone regulation required for healthy skeleton. Some nutrients are integral part of hormone producing mechanism. And their deficiency is related to low production of that hormone. Some nutrients like omega-3 fatty acids and vitamin D, are not naturally found in small amount. The good quantity supplement may also use for these nutrients. Chromium is commonly found in earth crust and also important mineral for human health. It is very important in insulin action and the deficiency is associated with failed glucose control. It is widely found in egg yolks, whole grains, cereals nuts, and coffee beans [3]. Vitamin D_3 is very essential in the primary biological regulators of calcium homeostasis and as a steroid hormone 1α, $25(OH)_2D_3$. It is produced photochemically in the skin from 7-dehydrocholesterol. The molecular structure of vitamin D is really resemble to classic steroid hormones (e.g., estradiol, cortisol, and aldosterone). It is important in balancing of other hormones. Vitamin E among other vitamins acts as anti-oxidant. It reduces oxidative stress and prevents hypothyroidism [16].

Probiotics The healthy and friendly gut bacteria are important to manage a healthy gut. The gut flora can reduce hormonal problems and enhanced levels of immunity. Different animal studies showed that supplementation with probiotics, prebiotic, and symbiotic has a visible effect on bone calcium, phosphate, and bone metabo-

lism. The dynamic interaction between microbiota and zinc was shown. Human studies have provided evidence of the influence of probiotic bacteria on parathormone, calcium, and phosphate levels and thus on bone re-absorption. Recent studies have produced new information mainly on the impact of the intestinal bacteria on the metabolism of calcium and iron. From a scientific perspective, the most urgent fields that remain to be investigated are the identification of all human gut microbes and new therapies targeting the interaction between intestinal bacteria and minerals [15, 17, 18].

Animals as well as human feed their gut bacteria, which are totally dependent on their host for giving the basic nutrients for growth and maintenance of the bacterial population. Food intake is pursuing by cephalic reflex-mediated moment of nutrients into the gut, which stimulate the gut–brain satiety pathways via releasing the intestinal hormones. Nutrient infusion into the large intestine activates immediate bacterial growth that lasts for 20 min. The dynamics of the formal nutrient-induced growth of bacteria are comparable to the dynamics of food-induced intestinal satiety hormone (for example, PYY) production. Bacterial metabolites and molecules, whose release directly depend on bacterial growth phases, control intestinal release of satiety hormones. Systemic bacterial molecules directly activate central appetite pathways that might integrate the energy status of both the host and its gut microbiota [17, 18].

Prevention and Treatment Strategies

Phytochemicals and Endocrine Health

Anti-oxidants prevent from free radical damage. The rich source of anti-oxidants are fresh vegetable including both green leafy spinach, asparagus, collard, cucumber, Kale, coriander, and bright colored vegetables such as bell pepper, cabbage tomato, and carrots. Polyphenols, alkaloids, and terpenoids found in fruits, vegetables, and fungi are helpful in balancing hormones [19].

Avoid or Restricts Food Toxins

Hormones are in state of constant fluctuations. Hormonal imbalance is epidemic these days due to lots of factors but the primary reason is the food of a person. The food industry is loaded with chemicals, colorants, preservatives, high amount of refined sugars. Fast foods also contain huge amount of salts and Tran's fats. All these chemicals can result in abnormal hormone. The avoidance of bad foods like lots of colorants processed foods and extra sodium is also important for making harmony among hormones [20].

Sleep Quality

A good quality 7–8-h night sleep has lots of benefits and helpful in refreshing the gland to help in production of normal hormones. Sleeplessness also known as insomnia may cause stress and irritability leading towards less immunity and poor performance of cognitive ability. This restlessness may also contributor in weight gain and low immunity [21]. Melatonin has positive and curative effect on all sleep disorders [22]. Sleep disorders are common among patient of chronic diseases. The change in hormone production is the reason behind disturbed and changed sleep pattern [23]. Some foods help in better sleep quality and reduce risk of insomnia. (Fig. 24.7) Alcohol and caffeine beverages can interrupt normal sleeping pattern. These chemicals must be avoided at bed time. Herbal infusion especially chamomile tea is proved for relaxing brain and body [24].

The significance of sleep to hormones and glucose metabolism was first recorded more than four decades ago. After that time sleep curtailment has become an endemic behavior in modern society. Obstructive sleep apnea (OSA) is a common disorder in endocrine and metabolic problems. Experimental reduction sleep period reduces leptin (the satiety hormone), overproduction in the appetite-stimulating hormone which is ghrelin, and increases hunger and appetite [22, 25].

Fig. 24.7 Foods helpful in better sleep

Stress Management

The stress is meaningful for human and animal survival and protection of the body. However, in modern society, some of these bodily responses may cause disservice rather than protection. Chronic stress directly or indirectly damages the mental and physical health [26]. Oxidative stress is due the imbalance between the generation of free radicals and the competence of the body's anti-oxidant system. Free radicals are intensely unstable molecules, which are formed in the body during physiological metabolic processes. They contribute to react with other molecules (polyunsaturated fatty acids of cell membranes, proteins, polysaccharides, and nucleic acids), causing structural variation on a molecular basis, functional deformities of the cell and tissue damage [27]. An increased production of reactive oxygen species and reduces level of the anti-oxidant system in patients with hyperthyroidism, and particularly in patients with hypothyroidism is seen. These findings proved that thyroid hormones contribute strong influence on oxidative stress and the anti-oxidant system [12].

Stress and anxiety can ruin the balance of life. Stress and anxiety are common problem for all ages in this era. Almost every person has experience during some stage of life. But chronic stress has ripple effect on mind and body. Anxiety even postponement or stop ovulation in females. In male population it results with low testosterone level [28]. The treatment goal is to reduce negative impact of stress on body chemistry. It allows the body to regain control on mind and body. Stress management is the way of dealing with it through various mechanisms including:

- Calming the mind by de-stress
- Positively controlling emotions and challenges
- Peacefully handling the stressful circumstances [29]

Physical activity is the best solution to calm down stressful condition. It helps in normalizing body's response towards stress [29]. Physical activity can reduce stress hormones concentration and helpful in production of neurotransmitter Endorphins which helps in feeling good [30]. It also diverts the negative thoughts and emotions by diverting mind towards moment. Being active is helpful in reduction of physical tension of body. Furthermore, active lifestyle creates positive feeling along with self-confidence [31]. Physical activity does not mean to go for long race or doing gym for hours. Basically, any activity with moderate movement activity like riding a bi-cycle or playing has these beneficial impacts. Running or jumping breaks during the day also creates positive health benefits [32]. Exercise reduces stress, helping in lower cortisol levels and thus promoting a healthier hormone balance. Weight lifting and high intensity trainings have also been shown to directly increase testosterone levels in men [33, 34].

Yoga is also certified nonpharmaceutical method to combat with stressful condition. It may also be complementing to drug therapy to treat stress originated from physical health ailments. Therapeutic benefits from yoga may be attained from different asanas(positions) including niyama, yama, pranayama, pratyahara, dhyana,

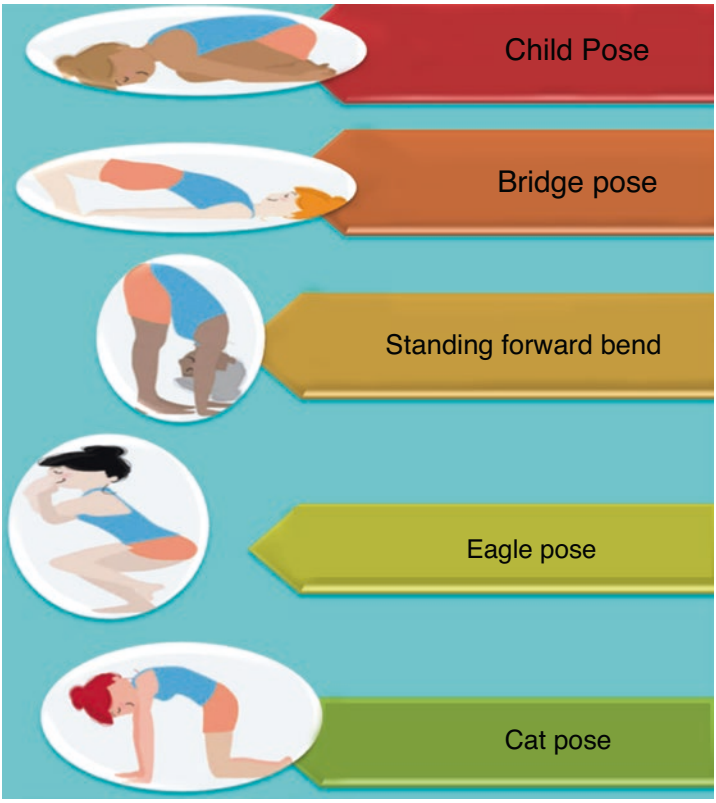

Fig. 24.8 Different yoga poses for stress relieving

and samadhi. In fact, yoga is a condition of deep conscious state of individual's conscious level (Fig. 24.8). Yoga practice leads to the self-actualization or self-discovery. This is a holistic approach of complete social, physical, mental, and spiritual harmony with nature. It leads to purity of mind and soul [35]. Meditation activities are helpful for relaxation, self-awareness, improve cognitive flexibility, and control of emotional reactions. By all these mechanisms yoga makes man strong to bear physical stress [11]. Stress reducing foods also helpful for its management. These foods includes oranges, oats, coffee, chocolates, banana, fish, spinach, broccoli, walnuts, eggs, flaxseeds, turkey, whole grain, probiotics, and tea [36].

Reduce Exposure to Environmental Toxins

Toxins in environment can cause hormone disruption in body. After exposure with these toxins body tries to eliminate them. Sometimes body fails or even do not find mechanism to eliminate and then starts to store in the body. This will result in toxic

body inner environment. The best solution is to avoid the toxin exposure of body by using different possible ways. Food packing material, unnecessary usage of drugs, exposure to chemicals, and extra sunlight can be controllable environmental toxins. A healthy gut through fermented foods and probiotics has ability to maintain, sustain, and correct hormone in normal production range [37].

Good Sleep

Book reading at bed time is helpful for peaceful and quality sleep at night. Reducing screen time at night is also a helpful tool for insomnia. Smocking, caffeine beverages, and certain drugs also hinder sleep quality. They must be avoided during night to promote better quality of sleep [38].

Stress Management

Stress produced free radicals and hormonal resistance by organs. To avoid stress, a person must have a positive physical hobby rather than electronic. That hobby may be a book reading, gardening, cooking, friends meet up or any activity that have pleasure and positive effect on emotions [39]. Positive social connections are also helpful for normalizing hormones [40].

Endocrine Health and Toxins

Make up especially eye colors cause dry eye syndrome due to their hormonal blocking effect among women [41]. House hold chemicals, kitchen cleaners, alcohol, and food preserving chemicals must be reduced for prevention and restricted for treatment. The limited use of plastic utensils and microwave ovens can prevent from exposure with EDC to safe extent [42]. Smocking and alcohol cause auto-toxicities through various mechanisms. These chemicals initiate auto immunity and create number of diseases due to weak immunity. Similarly polluted air directly contribute endotoxins [43]. Dietary fibers and some special elimination diets are helpful for removal of toxins [44]. Including dietary fiber in daily meals have preventive as well as therapeutic effect against the cosmetics and environmental pollutants [44]. Avoiding or limited exposure to endocrine disrupting chemicals is the best solution for harmony among hormones.

Conclusion

Toxic environment creates a toxic body by producing and storing environmental pollutants. These chemicals and adulterants cause serious health issues by mimicking naturally producing hormones and adversely effects endocrine system. The synchronization and balance production of hormones by endocrine glands is crucial of heath maintenance. Balance and nutritious food along with active life style are important to maintain normal level of hormones. Sleep quality and relaxing environment also play important role on emotional and hormonal health.

Conflict of Interest Nothing to declare.

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Chapter 25
Role of Nanoparticles in the Management of Metabolic Disorders

Zoya Iqbal, Muhammad Ibrahim, and Ghulam Murtaza

Abstract Nanotechnology, a rapidly flourishing field has emerged as cutting-edge technology in the twenty-first century indicating a promising future. Over the past decades, explosive research efforts have resulted in the development and evaluation of a plethora of nanoparticles for potential applications such as diagnosis and therapy. Hence playing a crucial role in research and development (R and D) and driving a revolution. NPs have garnered the interest of researchers due to their controlled and sustained-release features, biocompatibility, and subcellular size as well as extensively studied in pharmaceutical and medical fields. Since, the mode of fabrication plays a pivotal role; therefore, several techniques have been employed to prepare the NPs of desired characteristics for a particular application, i.e. the properties of NPs can be optimized based on the preparation method. Thus, various techniques have been employed to formulate NPs over the past two decades.

Keywords Nanoparticles · Diagnosis · Therapy · Sustained-release · Metabolic diseases

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Introduction

Nanotechnology is an interdisciplinary research field that has created a real hype about their great and unprecedented role in early diagnosis, accurate detection, and therapy of various diseases, including cancer. The ability of nanoparticles to present revolutionary interactions with biomolecules has revolutionized the therapy [1]. Research on nanoparticles (NPs) has flourished in the past decades. The field of nanotechnology is being considered as the driving force behind consequential improvements in health as well as in the industrial revolution. NPs' drug delivery systems are an intriguing field that has drawn the attraction of innumerable researchers and engaged them in exploring the potential of NPs as carriers for therapeutic, diagnostic as well as imaging applications [2].

NPs are defined as submicron-sized (10–1000 nm) solid drug carriers prepared from natural or synthetic biodegradable or non-biodegradable polymers, where the drug is either encapsulated within the NPs or adsorbed onto its surface [3]. NPs have been used to enhance and alter the pharmacokinetic as well as pharmacodynamic characteristics of several moieties leading to an ever-increasing research interest in utilizing NPs as drug delivery systems. NPs offer ingenious therapy by permitting targeted drug delivery and controlled drug release.

This chapter aims at summarizing various proposed techniques employed for the fabrication of NPs over the past two decades, great strides made in these methods over the last decades and highlight the diversity of these techniques with their advantages and limitations. It is remarkable that during past decades, noteworthy progress has been made which allowed stepping over the various milestones in improving existing methods leading to the emergence of techniques that permit the preparation of large batches of NPs in a reproducible manner. This chapter describes the comparison of NPs with other drug delivery systems, underlined the basic principles of each technique and the major factors that determine the NPs formation. Later part of the chapter presents the drying techniques, characteristics of NPs and their applications in drug delivery.

Advantages and Limitations of NPs

NPs have greater internalization as compared to the MPs [4]. In addition, NPs are appropriate for the delivery of drugs via intravenous (IV) route due to the small diameter of the capillaries (5–6 μm) as compared to MPs [5]. NPs show improved stability both in storage and in a biological system. Their preparation is relatively easy to scale up. NPs can fabricate a controlled release (CR) formulation. Following are various advantages of NPs:

- Enhance the aqueous solubility of hydrophobic drugs.
- Protect the drug molecules against degradation.
- It offers the possibility of a prolonged release of the drug.

- Prolong drug circulation time in the body [6].
- Enhance the bioavailability of the drug.
- Reduce both toxicity and adverse effects by providing targeted delivery of the drug.
- Decrease the drug side effects.
- Provide an appropriate form for numerous routes of drug administration, i.e. nasal, oral, intra-ocular, and parenteral.
- Allow rapid-formulation development.
- Ability to cross organ barrier, i.e. blood–brain barrier (BBB), and cell membrane.
- High drug loading and incorporation of the moieties without involving any chemical reaction; significant for preserving the activity of the drug [7].
- Show good potential for functionalization with various ligands and surface modification.
- Improved permeation through several biological barriers [8].
- Enhance the pharmacological as well as therapeutic effects of conventional drugs.
- Because of small size, NPs are able to bypass the BBB and function on the cellular level.
- Offers potentials of controlled release and targeting.
- The encapsulation of drug molecules into nanocarrier can prevent the degradation of the drug.

Following are the limitations of NPs: -

- Limited loading of drug and burst release.
- High surface free energy due to small size results in aggregation and agglomeration, secondary crystallization, and Ostwald ripening resulting in stability issues.
- Many NPs drug delivery systems have a too large size to extravasate in human tumors [9, 10].
- Particle-particle aggregation due to reduced size and large surface area poses difficulty in the physical handling of nanocarriers in dry and liquid states.
- Various techniques for the fabrication of NPs may not be suitable for large-scale production.
- Involve high development cost, hence pose the economic and financial barriers [11].
- Easy cellular uptake of NPs through the biological barriers and cellular membranes can cause cellular dysfunction [12, 13].
- Carrier systems themselves may inflict the harms to the patient [14].
- Furthermore, owing to their unique characteristics, including high surface/volume ratios, nanomaterials are reactive or catalytic and thus can be possibly toxic.
- Show low biological half-life due to quick removal of NPs by the reticuloendothelial system (RES).
- Traces of residual organic solvents cause toxicity.
- Possibility of poor targeting.

Materials Employed for the Fabrication of NPs

They can be fabricated by means of several materials, i.e. metals (silicon, silver, gold, and platinum), lipids, and polymers. Virus-based NPs have also been developed by researchers for tissue-specific targeting [15]. Polymers have a significant role in the delivery of low molecular weight moieties and macromolecules due to incredible development in the polymer chemistry arena. Synthetic and natural polymers are two broad classes of polymeric materials.

The selection of suitable materials for the formulation of NPs depends upon consideration of the features [16], as mentioned below:

- The desired particle size for the delivery system.
- Stability and aqueous solubility of drugs.
- Antigenicity of the polymers.
- Toxicity profile and biocompatibility of polymer.
- The desired surface features of the particle.
- Desired drug release characteristics.
- The degree of polymer biodegradation.

Methods of NPs Fabrication

Emulsification-Solvent Evaporation Method

Water-immiscible, volatile organic solvent, e.g. dichloromethane was used for the dissolution of the polymer. Then, the drug is encapsulated either by dispersing/dissolving it into a polymer organic solution to form organic phase and this organic phase is then added as droplets in external phase containing surfactant, i.e. pluronic, tween 80, and polyvinyl alcohol (PVA) solution to prepare o/w emulsion. Nanospheres are formed on the precipitation of polymer, later organic solvent is removed by stirring or rotary evaporator under reduced pressure (Fig. 25.1) [17]. Several parameters influence the particle size, i.e. temperature, rate of stirring, conc., surfactant nature, and the viscosity of the organic and aqueous phase. In a study, polycaprolactone (PCL) and Poly-L-lactic acid (PLLA) based polymeric nanoparticles (PNPs) were the smallest particles reported having a diameter of 76 nm in the case of PLGA with sodium dodecyl sulfate (SDS) as being employed as a surfactant. On the other hand, PCL NPs were reported with the largest particles [18]. It is not feasible to encapsulate hydrophilic compounds with high loading efficiency by commonly utilized methods/single emulsion technique (Fig. 25.2) because of the rapid partitioning of the moieties to the outer phase. To overcome this issue, a double emulsion technique (Fig. 25.3) is usually employed [19]. This simple method has flexibility in the selection of the solvent and the surfactant for the

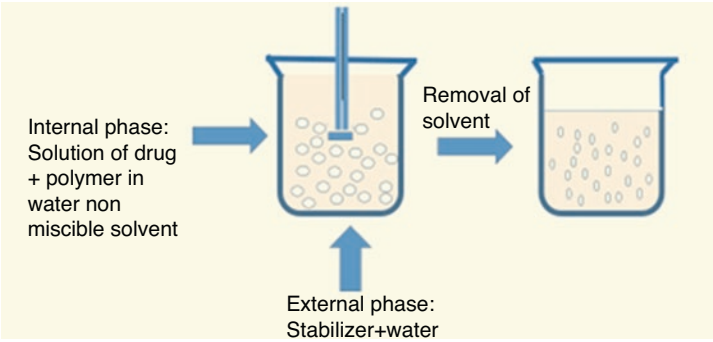

Fig. 25.1 Illustration of the emulsion solvent evaporation method

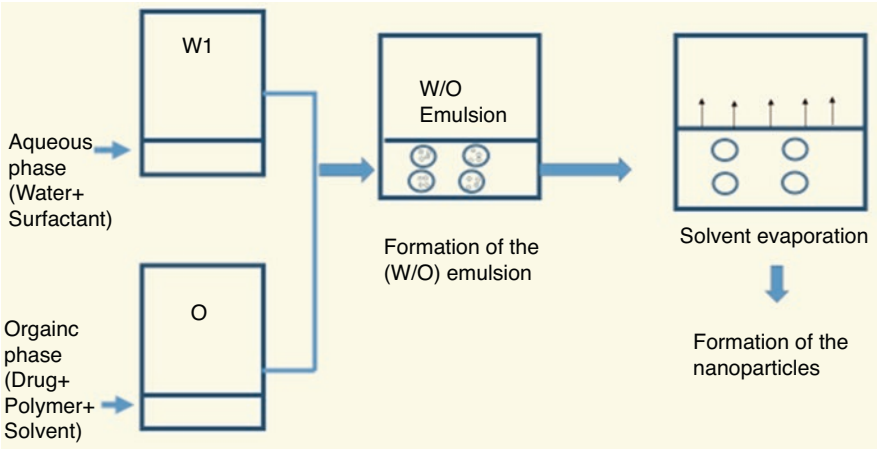

Fig. 25.2 An illustration of single emulsion solvent evaporation technique

formulation and is applicable to a variety of polymers. It exhibits a better particle size distribution and does not rely on diffusion to formulate the NPs. There is the flexibility in the solvent and the surfactant used for formulation emulsification-solvent evaporation technique.

This method employs sonication or high energy homogenizer. Though these processes are feasible to be carried out for the laboratory scale production, the production at a large scale requires substitute methods employing low-energy emulsification methods. The use of toxic solvents is involved in this approach. In addition, the presence of residual surfactants [20], time-consumption, and chances of coalescence of the nanodroplets while evaporation may influence the morphology and final particle size [21].

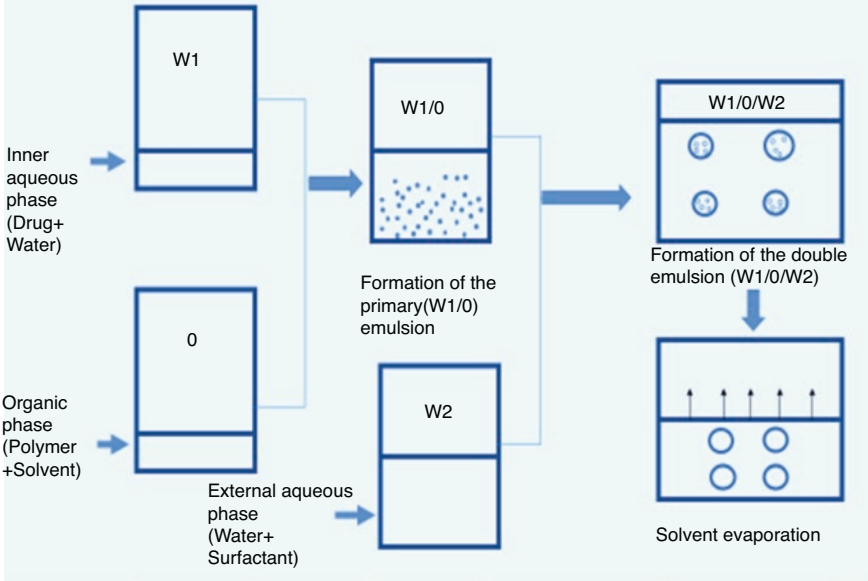

Fig. 25.3 An illustration of double emulsion solvent evaporation technique

Nanoprecipitation Method

It is feasible, reproducible, and widely employed techniques for the fabrication of nanospheres. This approach is also named as the *solvent displacement* method [22] and was first reported by [23]. This approach has been employed for the loading of moieties (hydrophobic and hydrophilic). This approach employs polymer, solvent for the polymer, and non-solvent for the polymer.

To improve the drug entrapment efficiency (EE) or to reduce the size of the NPs, a modified nanoprecipitation method was used employing a co-solvent. The choice of the organic solvents as polymer solvents (hexane, ethanol, dioxane, or acetone) depends upon the characteristics of the solvent, i.e. water miscibility and easy removal by evaporation. Therefore, in this approach the solvent that is usually employed is acetone. The first step is the dissolution of the polymer and drug in a water-miscible internal phase having intermediate polarity, e.g. ethanol/acetone. The second step is the dropwise injection of the organic phase having drug and polymer into a stirred external phase having a surfactant. NPs are formed instantaneously during the spontaneous diffusion of the organic phase into the external phase**,** as revealed in Fig. 25.4. The common solvents used (ethanol, THF (tetrahydrofuran), and acetone) are usually removed by the evaporation process under reduced pressure since their boiling points are lower than that of water [24]. Several polymeric materials, i.e. PCL [25], PLA (polylactic acid) [26], and PLGA [27, 28] have been employed in this technique.

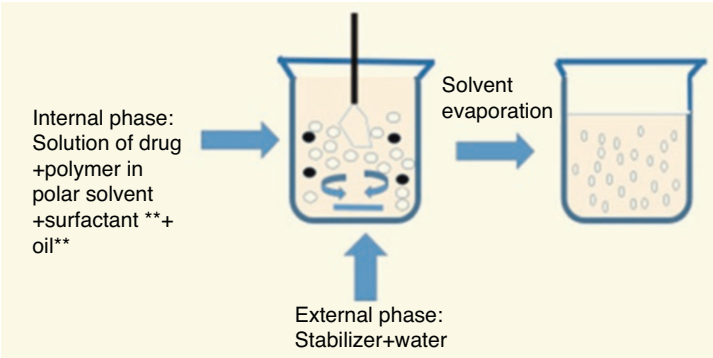

Fig. 25.4 Diagrammatic representation of the solvent displacement technique

The important aspects affecting the physicochemical characteristics of the formulated NPs are (1) organic solvent with the external phase miscibility; (2) the degree of polymer solubility in the organic solvent; and (3) the conc. of the polymer in the polymer solvent. It is a relatively simple technique that involves the use of nontoxic solvents and does not involve the use of high shear stress, surfactants, or stabilizers. Evaporation of solvent can be time-consuming. Its other shortcoming is its low encapsulation efficiency (EE) of hydrophilic drugs.

Emulsification-Solvent Diffusion

This technique is also named as emulsification-solvent displacement. Drug loaded controlled release NPs with desired characteristics can be formulated by solvent evaporation, solvent extraction, solvent diffusion, or any modification in the basic principle of the emulsification process [29]. This low energy method has been usually employed for the formulation of the solid lipid NPs (SLN) [30]/SLNs exhibit a novel potential class of colloidal drug carrier systems [31]. The drug and polymer are generally dissolved in a partial water-miscible organic solvent, e.g. propylene carbonate, methyl acetate, isopropyl acetate, ethyl acetate, butyl lactate, benzyl alcohol, and methyl ethyl ketone. The external phase may comprise of surfactants, i.e. pluronic, PVA, and sodium taurocholate, while the internal phase sometimes has emulsifiers such as soy lecithin (Fig. 25.5). The first step is the dissolution of the polymer in an organic solvent that is partially miscible with water, after saturation of this phase with external phase to achieve the primary thermodynamic equilibrium of liquids, then dilution with a volume of water in excess to cause the diffusion of the organic solvent out from the internal phase droplets to cause the polymer precipitation to lead to the fabrication of the NPs as shown in Fig. 25.5. Prior to the removal of the solvent by evaporation, the organic solvent should first diffuse out into the aqueous phase [32]. Finally, the organic solvent is removed depending upon the evaporation temperature of the organic solvent.

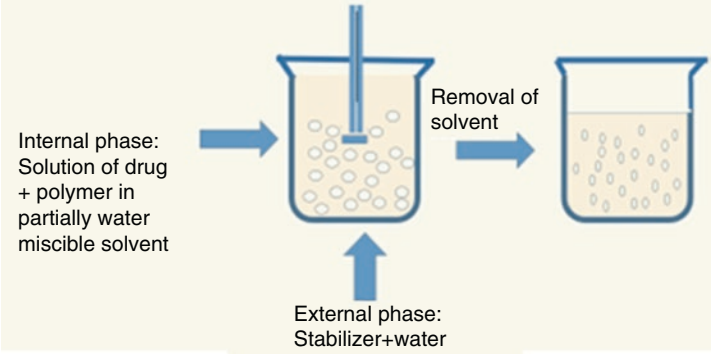

Fig. 25.5 Diagrammatic presentation of the emulsification-solvent diffusion approach

The generally used techniques to prepare PLGA NPs are emulsion solvent diffusion [33], nanoprecipitation [34], and emulsification-solvent evaporation [35] but in comparison with nanoprecipitation, emulsification-solvent evaporation (ESE), and emulsion solvent diffusion (ESD), especially modified spontaneous emulsification exhibits better properties, e.g. high drug entrapment efficiency as well as narrow size distribution [36]. Its advantages include improved EE for poorly water-soluble drugs, narrow size distribution, rapid organic solvent extraction, good batch-to-batch reproducibility, no homogenization required, simplicity, and feasibility of scale-up. The time needed for the evaporation of the excess volume of water which poses the escape of hydrophobic moieties while preparation must be adequate.

Salting out Method

The phenomenon involved in this technique is that the addition of an electrolyte decreases the solubility of the nonelectrolyte in the water [37]. This technique is the modification of the solvent emulsification technique. This technique includes the utilization of salting out agents for the separation of two-phase, i.e. water-miscible solvent and external phase (Fig. 25.6). Polymer and drug are dissolved in an external phase, generally, acetone later added into an aqueous solution containing high conc. of salting out an agent (calcium chloride as well as magnesium chloride with a surfactant, i.e. polyvinyl pyrrolidone) with stirring to prepare an oil-in-water (O/W) emulsion [38]. The adequate volume of water is needed for the dilution of (O/W) emulsion resulting in increasing the diffusion rate of organic solvent to the external phase, consequently formulating nanospheres. Commonly employed electrolytes in this technique are calcium chloride, magnesium chloride, and magnesium acetate [39, 40]. This approach has several advantages, as discussed below:

- Avoid chlorinated solvents as well as surfactants.
- Reduction of stress for protein encapsulants.

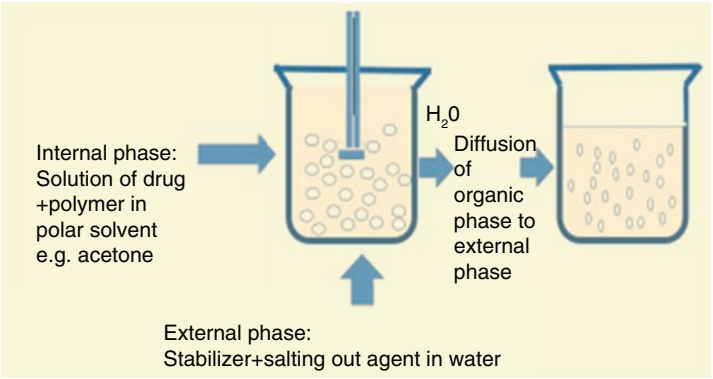

Fig. 25.6 Diagrammatic representation of the salting out method

- Use for heat-labile substances because high temperature is not needed in this technique.
- High encapsulation efficiency.
- High yield and purity.
- The simplicity of the operation.
- Easy scaling up.

The disadvantages of this modality are stated below:

- The possibility of incompatibility between salts and drugs.
- Exclusive applicability to lipophilic drug.
- Needs extensive NPs washing steps to achieve purity.

Coacervation Phase Separation

Fong in 1979 was the first to report the coacervation method to formulate polyester microspheres [41] and its modifications are employed today for the fabrication of NPs. This method involves the precipitation of the polymer. Precipitation happens on adding the third compound to the internal phase or it can be due to some other physical ways. Two liquid phases have to be formed, coacervates rich in polymer and polymer depleted supernatant liquid phase. This technique involves two steps, firstly, depending upon the solubility parameters of the polymer, liquid droplets of the polymer from the external phase are formed and secondly, the removal of the polymer solvent subsequently causes the hardening of the polymer droplets.

Organic solvents employed as the solvent, cooperating agents, and hardening agents are dichloromethane, isopropanol, and heptane. This method can be employed to entrap both hydrophobic as well as hydrophilic drugs but with varying drug EE. The hydrophilic drug is solubilized in the aqueous phase and later, this external phase is added to the internal phase containing polymer (W/O emulsion). On the

other hand, the lipophilic drug is dispersed or dissolved in a polymer solution in an organic solvent. This technique is well known for the preparation of PNPs but employing it for the preparation of lipid NPs is quite innovative [42, 43]. SLNs of cyclosporine were prepared by this technique [44]. This technique prevents partitioning out of the drug into the disperse phase. Moreover, it is a feasible and accessible technique that does not require a solvent [42]. Its only disadvantages are the residual solvent content particularly when the organic solvent is employed as a hardening agent.

Polymerization Technique

This method includes the fabrication of NPs by the monomer's polymerization in an external phase. The polymerization method can be subdivided as stated below:

Emulsion Polymerization Method

A scalable and rapid technique for the production of NPs. Based on the characteristics of the external phase employed, it can be further characterized as: continuous aqueous phase method and continuous organic phase method.

Continuous Organic Phase Method

It includes the diffusion of monomer's solution into an inverse microemulsion/emulsion or in a monomer's non-solvent. This method involves employing toxic organic solvents, initiators, and monomers which need to be removed from NPs so it is not a popular technique. Therefore, other techniques have gained more attention because it is a laborious process.

Aqueous Continuous Phase Technique

This technique uses water as a continuous phase and also to dissolve the monomer. This method does not need the use of the emulsifier/surfactants. Numerous approaches are employed at the beginning of the polymerization reaction. In the continuous phase, initiation begins on the collision between the initiator (free radical/an ion) and the dissolved monomer molecule. While the polymerization can be started by strong visible light or ultraviolet or high-energy radiation (γ-radiation). Polymerization initiates through the anionic polymerization mechanism on the collision between the monomer molecules and radicals. Phase separation happens and NPs are formed before or after the polymerization process termination. It is an easily scalable and the fastest method for the preparation of NPs. The disadvantages of

this approach are the involvement of toxic organic solvents (monomers, initiator, and surfactants), difficult processing, reactive residues, unreacted monomers, and the risk of the formation of unwanted oligomers.

Interfacial Polymerization

It employs polyaddition and polycondensation methods. It has been extensively employed for the preparation of microcapsules or oily core nanocapsules [45].

Interfacial Polycondensation

This technique involves the condensation of the hydrophilic and lipophilic monomer, e.g. diethylenetriamine and phthaloyl dichloride, respectively, to prepare nanocapsules either in the presence or absence of stabilizer. The internal phase is water-miscible organic solvent having a hydrophobic polymer, whereas the external phase contains a surfactant and hydrophilic monomer. The first step is emulsification and it comprises the spontaneous formation of an emulsion. The second step is the polymerization step. Polycondensation reaction takes place at or in a thin region adjacent to the interface of two immiscible liquids which then leads to the formation of nanocapsules [46, 47]. This method involves less concentration of surfactants. By varying, the concentration of the monomer thickness of nanocapsule can be modulated. The disadvantages of this modality are stated below:

- Low concentration of surfactants.
- Restricted to hydrophobic drugs encapsulation.
- Requires purification.
- Alteration of the thickness of the nanocapsule by fluctuating the monomer conc.

Miniemulsion Polymerization

This technique (Fig. 25.7) contains an initiator, water, monomer mixture, co-stabilizer, and stabilizer. Miniemulsion polymerization technique is different from the emulsion polymerization in terms of using a low molecular weight compound as the co-stabilizer to critically stabilize it and also involving ultrasound (a high-shear device), to achieve an interfacial tension <0 and steady-state [48, 49].

It is an effective technique for the formulation of polymer nanostructures [50] and has gained considerable attention. Emulsion polymerization appears similar to micro-emulsion polymerization in starting conditions and the mechanism of polymerization as both techniques can formulate high molar mass colloidal polymer particles while kinetically completely different. The microemulsion polymerization technique produces polymer particles having small size and significantly a smaller number of chains in a particle (Table 25.1). This technique involves the addition of

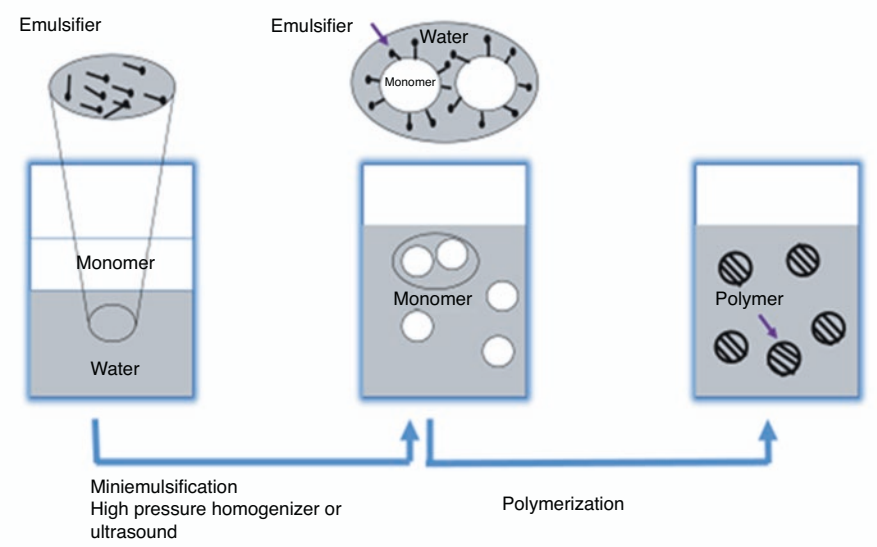

Fig. 25.7 The principle of miniemulsion polymerization

Table 25.1 Miniemulsion vs microemulsion

Type	Miniemulsion	Microemulsion
Key characteristics	Thermodynamically unstable system [104] Stable up to hours to months [105]	Thermodynamically stable dispersion having an interfacial tension between internal/external phase near to zero [106] Stable for an infinite period of time under constant storage conditions [107]
Diameter ranges of droplet	20–200 nm [108], narrow size distribution is required	~10–500 nm [109] Narrow size distribution Spontaneous formation
Equipment requirements	High-pressure homogenizer, ultrasonicator, spontaneous emulsification process, colloidal mills	Simple mechanical stirrer

a hydrophilic initiator to the external phase of a micro-emulsion (thermodynamically stable) having swollen micelles. The polymerization process begins from this spontaneously formed thermodynamically stable state and based on increased amounts of surfactants, which have an interfacial tension interface ~0 at the internal-external phase interface. Surfactants completely cover the particles as the surfactants are used in high amounts. The advantages of miniemulsion and microemulsion are as given below:

- miniemulsion and microemulsion are considered better than classical emulsions [17, 51].

- Higher stability as compared to classical emulsions [32].
- NPs with better-controlled particle size can be obtained.
- More reproducible methods of fabrication.

Production of NPs *Employing Supercritical Fluid (SCF) Technology*

SCF has been employed as another fascinating means to formulate NPs of biodegradable nature. This method is considered environmentally safer because unlike conventional techniques it avoids the need for toxic organic solvents. It is classified into two techniques depending upon the role of the supercritical CO_2 in the method as either a solvent or an anti-solvent for rapid expansion of supercritical solutions (RESS) or as an anti-solvent for supercritical anti-solvent process (SAS), respectively [52].

Supercritical Anti-Solvent (SAS)

A supercritical anti-solvent miscible organic solvent such as methanol is used for the dissolution of the solute of interest. The solute must not be soluble in supercritical anti-solvent. The supercritical carbon dioxide ($CO_{2)}$ is pumped into a precipitation vessel from high pressure to a certain pressure. Later, this solution containing an active pharmaceutical ingredient (API), the polymer is sprayed via a nozzle in the reactor (Fig. 25.8) [53–56]. The extraction of organic solvent by the SCF results in prompt solute precipitation as NPs [57]. In this technique, the solvent power of a polar organic solvent containing an active pharmaceutical ingredient (API) and the polymer is decreased by saturating it with CO_2 at supercritical conditions. The CO_2 results in the precipitation and recrystallization of the API [58]. This approach requires a long washing time before the agglomeration/aggregation of NPs. This issue can be resolved by enhancing the mass transfer by achieving the intense mixing of supercritical anti-solvent and the solution. Another disadvantage of this technique is the residual toxic solvent in the product [59]. The advantages of this approach are stated here:

- Feasible for the production of NPs on large scalable [60].
- Applicable to a wide range of APIs and polymers.
- Continuous process.
- Rapid contact between anti-solvent and the polymer solution fasten up the nucleation and growth processes, therefore forming smaller particles.
- Performed at room temperatures, hence prevents thermal degradation of the NPs [61].
- Easy removal of the supercritical fluid from the system by lowering the pressure or depressurizing ([61–63].
- Formulate drug-encapsulated NPs having high polymorphic purity [64].

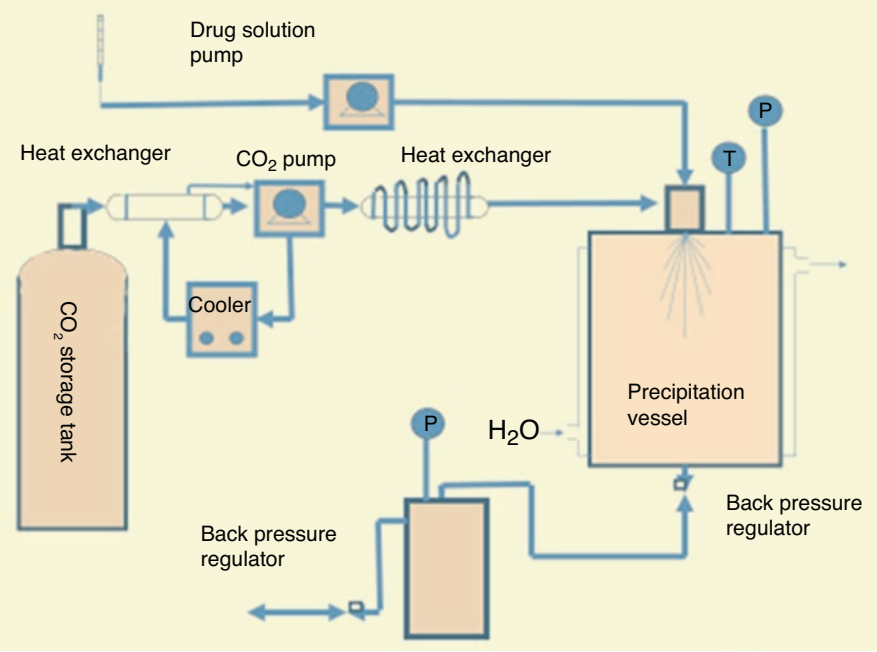

Fig. 25.8 Schematic diagram of the SAS process

In this approach, the parameters affecting the particle size [65] are the pressure of CO_2, the solubility of the moieties in the SCF mixture, organic solvent polarity, rate of agitation of the feed dispersion, and the polarity of the solute. The increase in the pressure will increase the solubility of the compound in the SCF, in turn reducing the degree of supersaturation in the precipitation vessel, hence resulting in a marked size increase [65].

Rapid Expansion of Critical Solution (RESS)

It involves the dissolution of the polymer and drug in the SCF. Later, the rapid expansion of SCF into a region of low pressure through a nozzle leads to the precipitation of the solutes as NPs. In RESS, the morphology and size of the particle are considerably influenced by the conc. and the level of saturation of the polymer [66]. It is an environment-friendly and high-quality technique that shows the high purity of NPs and shows suitable technological and biopharmaceutical characteristics. The method is not cost-effective and it needs extensive recycling measures to lessen energy cost. It involves an initial high capital investment for equipment. The raised operating pressures necessitate the use of high-pressure equipment. There is a difficulty in the dissolution of highly polar compounds in supercritical CO_2.

Dialysis

This technique involves a solvent displacement mechanism but in contrast to the conventional nanoprecipitation method (Fig. 25.9). It includes additional tools such as a dialysis bag/semi-permeable membrane [67]. Polymer, drug, and surfactant are dissolved in the same organic solvent and are loaded into a proper molecular weight cutoff dialysis bag [68]. A solvent which is non-solvent of the polymer but miscible with the polymer solvent is used for dialysis. The dialysis membrane with suitable molecular weight cutoff will act as a physical barrier for the polymer but will allow the movement of the solvent inside. Hence, the loss of solubility of the polymer and aggregation of the polymer will occur resulting in homogeneous suspensions of NPs [21]. This nanoprecipitation method has been successfully employed to entrap several drugs such as doxorubicin, retinoic acid, paclitaxel, curcumin, gentamicin, clonazepam as well as various hydrophobic drugs [69–74]. Furthermore, drugs having hydrophilic nature such as proteins and peptides show decrease solubility in the organic phase. Therefore, this technique cannot be employed for the loading of drugs of hydrophilic nature into NPs. It is an effective and simple technique for the fabrication of small, finely distributed polymeric NPs [67]. It does not involve the use of any sophisticated material. An increased concentration of NPs (by factors from 10 to 50) in suspension can be achieved from initial formulation values without involving NPs aggregation [32]. Before and after NPs formation drug easily releases from the dialysis membrane [75].

Separation Techniques of NPs

Depending on the technique of fabrication, separation of NPs from the free drug and polymer aggregates has been achieved by using different methods, such as ultracentrifugation, dialysis, cross-flow microfiltration, diafiltration, gel filtration, and dialysis.

Stability of NPs

It is influenced by several physical and chemical characteristics, as discussed below:

Physical Stability

The opposition of the gravitational forces by Brownian motion prevents the sedimentation of the colloidal size particles, therefore the suspended particles of different contents, zeta potential, and morphology randomly collide resulting in settling

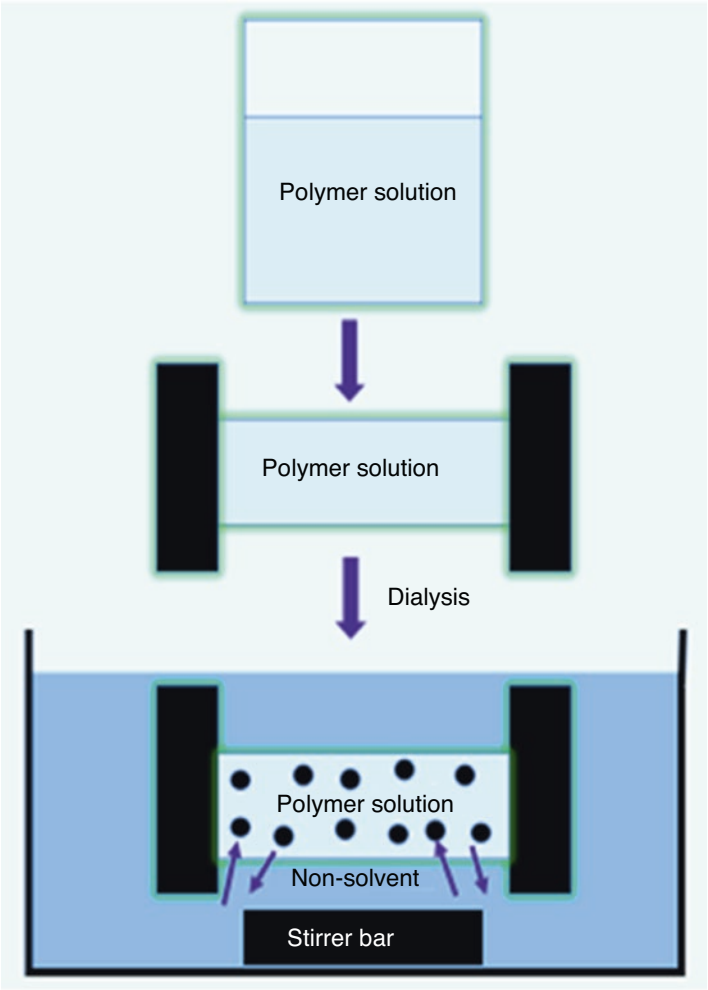

Fig. 25.9 Diagrammatic illustration of an osmosis-based method for the preparation of PNPs

of the particles due to agglomeration. The selection of an appropriate stabilizer is required to prevent this phenomenon, for example, phospholipids, dimethylamine borane (DMAB), PVA, and pluronic.

Chemical Stability

The features affecting the stability of NPs are the chemical stability of encapsulated moieties, the molecular weight of the polymer, polymer nature, and the storage conditions, including temperature and pH. The temperature of 4–50 °C is consid-

ered optimum for the storage of biodegradable polymeric NPs for enhancing the NPs stability.

Lyophilization of NPs

It is the most usually employed approach for the removal of water contents from the NPs. The principle of this technique is the sublimation and desorption process by which it removes water from a completely frozen material under vacuum. Cryoprotectants are added in the product prior to freeze drying to prevent the NPs from desiccation stresses. Commonly used cryoprotectants are mannitol, trehalose, glucose, fructose, lactose, and sucrose. These saccharides act as spacing matrix and prevent agglomeration of NPs. Freeze drying is generally performed at a temperature less than the glass transition temperature (Tg) with the aim to immobilize the particles within the glassy matrix of the freeze-drying agents.

Physicochemical Characteristics of NPs

Particle Size

The size of NPs influences the degradation of the polymer as well as the release of the drug. NPs can cross the BBB since NPs have higher internalization potential as compared to the MPs. Particles of larger sizes localized in tissue epithelial lining, while NPs can cross the submucosal layers. Nanotechnology is at the forefront of the development of novel materials. Regardless of the diversity in the application of NPs, their performance depends on the particle size, morphology, and surface properties. Therefore, NPs characterization is a critical step in nanotechnology R & D. Various methods have been employed for measuring, detecting, and characterizing the nanoparticles. The selection of the method is based on the kind of sample, desired information, time limitations, and the cost of sample analysis. Particle size furnishes imperative information about NPs, it is one of the essential determinants of biodistribution as well as clearance parameters of the NPs in target tissues. The most crucial parameters among all of NPs' characterization are particle size distribution and morphology. The size and morphology of NPs are determined by electron microscopy. Numerous tools have been employed for NPs size measurement. Some of them are stated below:

Scanning Electron Microscopy (SEM)

This technique is arguably famous for enabling size, morphological and surface analysis of NPs with direct visualization. Electron microscopy-based techniques have several advantages in evaluating the size and morphology, at the same time

they have disadvantages of offering limited information regarding size distribution as well as true population average. To perform SEM analysis, the NPs solution is first required to be converted in form of dry powder followed by mounting it on a holder to coat with gold (conductive metal) by employing a sputter coater, leading to the analysis of the sample by using the probe. Interaction of electron beam with sample generates various signals. Appropriate detectors are applied to analyze these signals. It is necessary that NPs have the ability to endure vacuum as well as the electron beam which can cause degradation of the polymer [76]. Results obtained by SEM and dynamic light scattering for size are comparable. These techniques have some disadvantages such as the sample preparation for SEM is laborious, expensive, besides this, often require supportive information regarding size distribution. A generalized representation of SEM is given in Fig. 25.10.

Dynamic Light Scattering (DLS)

It is also named as photon-correlation spectroscopy (PCS) and is considered the fastest and prevailing approach of particle size analysis [77]. DLS is extensively employed to ascertain the size and polydispersity (PDI) (Fig. 25.11). It is generally utilized to evaluate the size of the particles in suspension which are under Brownian motion, i.e. Brownian NPs in the nano as well as a submicron size range. This

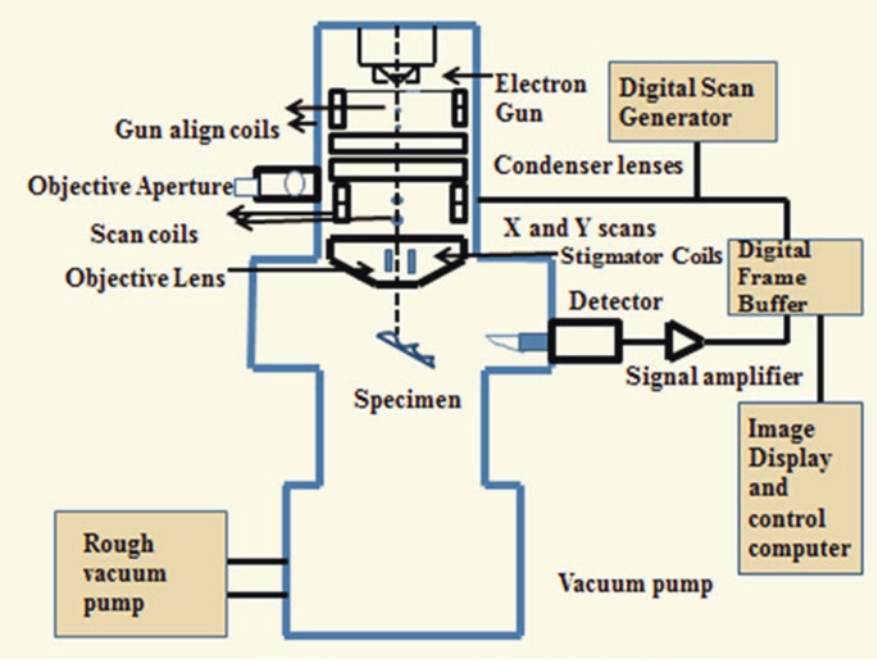

Fig. 25.10 Generalized representation of SEM

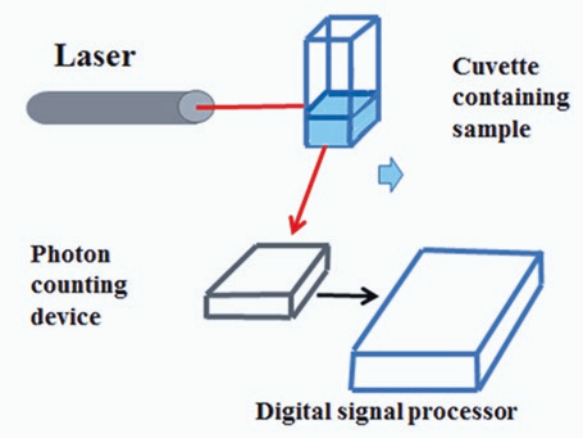

Fig. 25.11 Components of the DLS instrument

approach involves the exposure of the particle solution which is under Brownian motion to laser resulting in Doppler shift. This method is advantageous as the time required for the experiment is short as well as no extensive experience is required for routine measurements since it performs almost automatically.

Transmission Electron Microscope (TEM)

Although TEM and SEM have different working principles, the results achieved are often similar. Sample preparation for TEM is complicated and laborious as it requires an ultra-thin sample for transmittance of electrons which interacts with the sample while passing through it to obtain the surface properties of the sample. NPs sample is generally deposited directly on a grid or film (Fig. 25.12). NPs are fixed by utilizing negative staining materials, e.g. uranyl acetate or phosphotungstic acid, etc. or by plastic embedding so that they can withstand the vacuum of the system and it will also ease the handling of the sample. Another method is to embed the sample in vitreous ice and then keep at liquid nitrogen temperature.

Atomic Force Microscopy (AFM)

The most important advantage of AFM is that it enables imaging delicate biological and polymeric nanobodies besides microstructures because it does not involve any specific treatment to image non-conducting samples. It is convenient to use in various environments, e.g. aqueous solution, different solvents, in air, vacuum as well as other gases. It offers the most precise details of size and size distribution determination and it does not require any mathematical treatment [78]. Furthermore, size determined by the AMF approach gives a real image which aids to conclude the influence of different biological circumstances. It is the kind of scanning probe

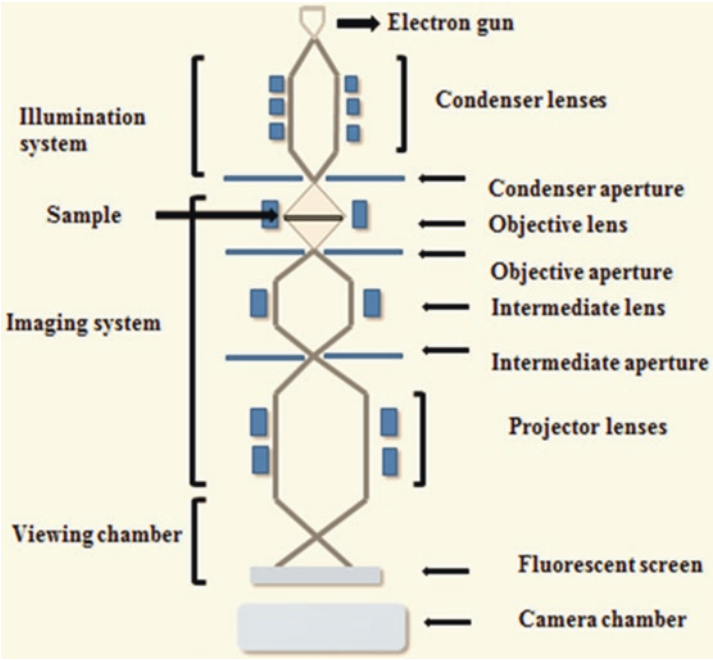

Fig. 25.12 The optical components of basic TEM

microscopy (SPM) having an ultra-high-resolution for size evaluation. This technique is advantageous in terms of providing three-dimensional visualization such as size, shape, and distribution. It also enables surface characterization. This technique involves the usage of an atomic-scale probe tip for scanning of submicron level samples. Based on the properties of the sample use for scanning, it has two different modes of operation either contact (also called static) mode or non-contact (also called dynamic) mode. In static mode, the tip of the probe drags across the sample surface and in each oscillation, the cycle moves completely away from the surface across the sample to generate the topographical map. On the other hand, in non-contact mode, the probe remains close to the sample surface.

Surface Charge

Zeta potential is an imperative feature of nanocarriers. It explains the physical stability of the particle, targeting capability, and in vivo distribution of NPs. It is the measure of the zeta potential and it is a significant pointer of the stability of particle. A minimum surface charge of *±30 mV is required* for the *physical stability of nanosuspension* by sufficient *repulsive forces.* It is *crucial to* take surface charge into *account* to *avoid* NPs *aggregation*. It is also a demonstrator of the loading of the

charged moieties within the center or surface adsorption. Neutral NPs have zeta potential ranging −10 to +10 mV, NPs with zeta potentials > +30 mV are regarded as strongly cationic. While NPs with a zeta potential < −30 mV are regarded strongly anionic. Because of the negative charge of most cellular membranes, zeta potential can affect the tendency of NPs to cross cellular membranes, cell wall disruption is generally caused by NPs having a cationic charge.

Surface Hydrophobicity

NPs with surface hydrophobicity on administration by intravenously (IV) are unavoidably removed by the *mononuclear phagocyte system* (MPS). To avoid the phagocytosis of NPs and their ultimate removal from circulation upon IV administration, the surface of NPs should be modified. To solve this problem two tactics are employed. One method includes the use of hydrophilic polymers such as chitosan, polyethylene glycol (PEG), or stabilizers, e.g. poloxamines or poloxamers for the surface coating of particles. The second method is employing biodegradable copolymers with hydrophilic blocks such as PLA-PEG. NPs surface modification with PEG gives stealth features to NPs; hence, they are not destroyed by macrophages, therefore, named "stealth NPs." Surface hydrophobicity can be estimated by several approaches, as stated below:

- Contact angle determination.
- Hydrophobic interaction chromatography.
- X-ray photon correlation technique.
- Biphasic partitioning, adsorption of probes.

Drug Loading

The drug can be loaded by two approaches: the adsorption/absorption method and the incorporation technique. Encapsulation efficiency and drug content of NPs are affected by numerous factors, as described below:

- The molecular weight of the drug.
- Polymer–drug interaction.
- The solubility of the drug in the polymer matrix.
- The existence of end carboxylic groups.

Drug Release

Depending upon the nature of polymers (Table 25.2), polymeric NPs have distinguishing applications of the controlled and sustained release drug delivery [79]. Several factors influence the release of drug, i.e. desorption, the solubility of the

Table 25.2 Commonly employed polymers for the fabrication of NPs used in drug delivery

Material	Polymeric matrix	Active agent	Technique
Synthetic homo-polymers	Poly (lactide-co-glycolide) PLGA	Cefixime [110] Felodipine [111]	Nanoprecipitation
		Curcumin [112]	Emulsification and solvent evaporation
	Poly (lactide) PLA	Quercetin [26]	Nanoprecipitation
	Poly (acrylate) and poly(methacrylate)	Vancomycin [113]	*Emulsion solvent evaporation* method
Natural polymers	Chitosan	Curcumin [114]	Nanoprecipitation
	Gelatin	Methotrexate [115]	Emulsion solvent evaporation
	Alginate	ICD-85 [116]	Ionic gelation method
	Albumin	Albendazole [117]	Modification of the desolvation
Copolymers	Poly (epsilon-caprolactone)- poly (ethylene glycol) PCL-PEG	Octreotide [118]	Solvent evaporation method
	Poly (lactide-co-glycolide)- poly (ethylene glycol) PLGA-PEG	Docetaxel [119]	Nanoprecipitation method.
	Poly (lactide)- poly (ethylene glycol) PLA- PEG	Plasmid DNA [120]	Nanoprecipitation method

drug, particle-matrix degradation or erosion and drug diffusion. Small size NPs have burst release owing to the poor entrapment or adsorption of the drug to NPs surface. NPs of large size have sustained release and no burst release. Different approaches can be employed to assess the release of drugs in vitro using either the dialysis method, diffusion cell approach, or ultracentrifugation method.

Kinds of Biodegradable NPs

Various kinds of NPs are portrayed in Fig. 25.13.

Application of NPs

Nanotechnology has overcome a variety of limitations in drug delivery (Table 25.3). NPs are employed for both active and passive targeting in cancer therapy. NPs have edge over other delivery systems because of the following features [80]:

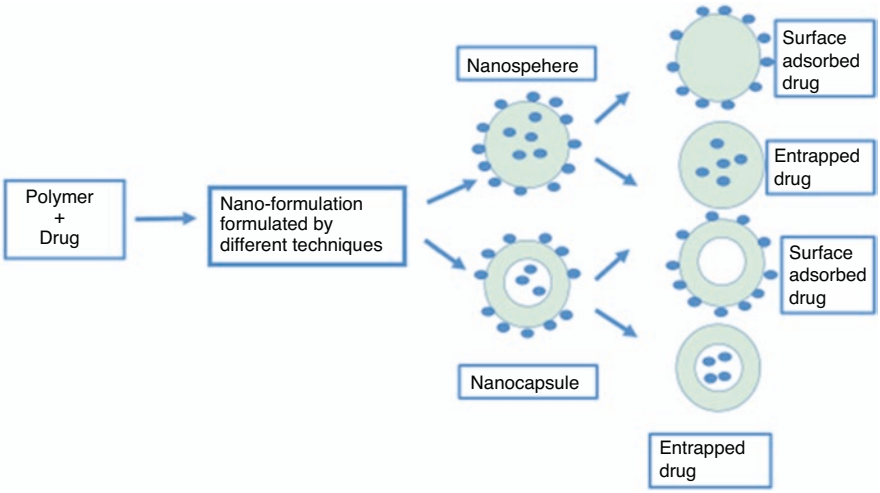

Fig. 25.13 Various kinds of NPs

Table 25.3 Summary of earlier investigations on the effects of NPs on several aspects of metabolic syndrome

Nanocarriers	Results	References
Chitosan nanoparticles	Useful for controlled drug delivery	[121]
PLGA-*b*-PEG nanoparticles	Prevented gain in body weight	[122]
Chitosan nanoparticles	Effective in lowering body weight and serum, lipid	[121]
Silver nanoparticles	Reduction in body weight	[123]
Pluronic F68, Squalene nanostructured lipid carrier	Enhanced clinical efficacy of lovastatin	[124]
Chitosan nanoparticles	For a prolonged time period efficiently decrease the blood pressure	[125]
Chitosan nanoparticles	Enhanced inhibition of the ACE	[126]
Polylactide nanoparticles	Digestion of LDL	[127]

- Reversion of multidrug resistance
- Proteins and peptides delivery
- Prevention from premature inactivation during transport
- Cell internalization
- Vaccine delivery
- Controlled release
- Decrease toxicity to healthy cells or tissues
- BBB targeting
- Efficient drug penetration
- Tumor targeting

Role of Nanocarriers in the Treatment of Metabolic Disorders

Triglycerides and HDL Blood

Currently, the use of nanoparticles (NPs) and beneficial or harmful effects pertinent to them have garnered more attention of the biomedical scientists. The effect of nanocarriers on the activity of lactate dehydrogenase was investigated and studies showed that short-term use of silver NPs was unable to alter the level of dehydrogenase enzyme [81]. Researchers have studied the toxic effect of different doses of silver NPs on lung tissues of rats. The alterations in some hematological and biochemical parameters in blood were measured after long-term oral administration of these NPs. No significant alteration in levels of blood cholesterol was observed, but a significant decrease in the level of triglycerides was measured after a period of 3 months [82]. A study has shown the influence of silver NPs on lipid conc. in broiler chicks and clinoptilolite on liver enzymes. They detected that the conc. of alanine aminotransferase as well as alkaline phosphatase enzymes reduced significantly. The concentration of triglyceride, VLDL, LDL, and cholesterol reduced while conc. HDL increased [83]. However, another study has presented that blood triglyceride was not influenced by manganese oxide NPs [84].

Diabetes and Blood Glucose

Metabolic syndrome is characterized by high blood glucose levels, high blood pressure, and triglycerides. A study has shown that 30 ppm silver NPs did not show any effect on the glucose level. Nevertheless, contradictory results are expected. Nanoparticles based strategies for insulin delivery are stated below:

Polymer Nanoparticles

These are colloidal particles having a size from 10 to 1000 nm and have unique characteristics such as biocompatibility and biodegradability. A recent study has exhibited that the dextran sulfate-chitosan nanocarrier based insulin delivery system has shown 85% association efficacy. No release of insulin was observed at pH 5.2 up to 24 h and a controlled release was observed at pH 6.8.

Dendrimers

Dendrimers are branched polymer systems range in size from 10 to 20 nm and have improved chemical and physical structure. PAMAM dendrimers offered the potential for insulin delivery by effectively improving the insulin absorption [85].

Ceramic Nanoparticles

Ceramic NPs are composed of silica aluminum, calcium phosphate, or titanium. They have advantages of biocompatibility, narrow size (<50 nm), ease of preparation, and good stability [86]. Ceramic NPs have shown the potential to protect the spatial features of insulin for demonstrating improved therapeutic effect [87]. These NPs efficiently protect the molecules from denaturation owing to the variations in the external temperature and pH.

Micelles

Micelles delivery systems are composed of a surfactant or *amphiphilic molecules, have a hydrophobic core and their size must be < 100 nm* [88, 89]. Stimuli-responsive micelles have exhibited their ability for controlled release of insulin for potential diabetes mellitus therapy [90].

Liposomes

Liposomes are spherical vesicles with the hydrophobic groups towards the center and hydrophilic groups arranged to the outer side of the molecule. Folic acid (FA) functionalized liposomes revealed nearly double hypoglycemia and about 20% relative bioavailability than insulin solution administered subcutaneously [91].

Abdominal Obesity and Fat Tissue

There is a gradual increase in the global epidemics of obesity as it is regarded as the fifth risk factor for mortality [92]. The death rate of a normal individual is 20% lower as compared to the obese person [93]. Obesity is associated with pertinent diseases, for example, type 2 diabetes, cardiovascular disease, bladder diseases, asthma, chronic lower back pain, and inflammation of the joints. In obese persons, a possible cause of overweight is the impairment of the metabolism of fat which causes the accumulation of fats in the body. A study has shown that gold NPs can be used as an approach for treating obesity and the diseases pertinent to obesity [94].

It has been suggested that NPs in the range of 1–2 nm are generally toxic, while gold NPs of diameter 15 nm are commonly inexpensive [95]. PLA-PEG NPs have presented increased expression of angiogenic and BAT markers, inhibition of weight gain and increased angiogenesis. Phospholipids and cholesterol-based liposomes have shown decreased deposition of the ectopic fat in muscle and liver. Furthermore, exhibited a decreased level of leptin, adipocyte size, and body weight [45]. Lipid nanostructures such as NLC-OEA/PAO-Cap formulations showed an ameliorating effect on glucose level, cholesterol, triglycerides profile and body weight.

Blood Pressure

Hypertension is a major global burden and a contributor to cardiovascular disorders, for example; stroke, peripheral vascular disease, cardiac failure, and myocardial infarction [96]. The antihypertensive drugs are facing the challenges of dose, bioavailability, and side effects which greatly influence their efficacy. Aliskiren loaded magnetic poly(D,L-lactide) NPs have shown improved blood pressure control in the hypertensive rats as compared to commonly administered drugs. Similarly, VP5-PLGANPs demonstrated an in vitro sustained release profile of VP5 and a prolong antihypertensive effect of 96 h with improved in vivo efficacy [97]. Nifedipine has short elimination half-life and rapid onset of action, and polymeric NPs of nifedipine have exhibited an increase in the bioavailability and median survival rate. Sustained drug release and a significant reduction in the blood pressure were also observed. Polymers that are widely employed for oral administration of high blood pressure of drugs are poly-caprolactone, chitosan, Eudragit, polystyrene, and hydroxypropyl methylcellulose. PLGA-NPs have shown 4 days of long-lasting reduction of systolic blood pressure than free drug and in vitro sustained release [98].

Various liposomal formulations have previously been developed successfully for hypertension in animal models. Liposomal preparation of vasoactive intestinal peptide (VIP) is a prominent example among all because of marked immunomodulating, vasodilatory, and antiproliferative properties [99]. Proliposomes encapsulated lercanidipine has shown long-lasting (about 24 h) as well as an immediate decrease in the SBP with a half-life of 6.95 h, as compared to the free drug (5.26 h) [100]. Another study has presented the advantage of reduced mean arterial blood pressure (by 50 mm Hg) and improved circulation time (5 h) [101].

Inflammation

Inflammation is considered to be the body's normal immune response and it can be triggered by several factors, such as damaged cells pathogens, and toxic compounds. The acute inflammation is because of the pathogenic, mechanical, chemical effects, which have a short duration of several hours to several days. Chronic inflammation is independent of stimulus and can produce various painful and debilitating symptoms. A study has shown the potential of G5-FA-MTX dendrimers in reducing arthritic inflammation parameters, for example, leg volume, knee swelling, bone resorption, cartilage damage, and body weight [102]. PLA-PEG NPs enhanced the anti-inflammatory response of rosiglitazone on macrophages by increasing drug uptake than the free drug [103].

Conclusion

The principle purpose of this chapter is to furnish an insight into the available techniques to formulate the fascinating polymeric NPs. It is of supreme importance to effectively consider vital parameters to select a method for NPs preparation. Methods of preparation of NPs have evolved based on several concerns such as economical scale-up by simplifying the process, enhance yield and entrapment efficiency by optimization and avoiding toxic reagents by utilizing techniques involving fewer toxic chemicals. Efficient entrapment of drug and easy large-scale production is of prime importance for applicability at the industrial scale. Innumerable techniques are available for fabrication of NPs and with advances in technology several important modifications have been made thus providing safe, feasible, and reproducible techniques for the formulation of drug-loaded nanocapsules and nanospheres. Depending on the physicochemical aspects of the drug, it has now become convenient to select an appropriate preparation technique and suitable polymer to enhance drug entrapment efficiency. The selected technique should curtail the loss of drug or responses. In this regard, the development of a method that enables the inclusion of drugs with no effect on their pharmacological activity establishes the elementary aim for nanotechnology. These efforts strongly unite the fascinating world of NPs research to commercial applications such as the management of metabolic diseases including diabetes and cancer.

Conflict of Interest Nothing to declare.

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Chapter 26
Intermittent Fasting for Treatment of Metabolic Disorders

Nizwa Itrat

Abstract Intermittent fasting is a powerful technique for regulating and normalizing hormones in their ranges especially insulin. It also reduces oxidative stress and inflammation which allows other hormones to work effectively. Intermittent fasting uses the power of circadian rhythms in correcting body's metabolic reactions and results in longevity. Intermittent fasting emphases on eliminating all refined carbohydrates and fructose from daily routine and on eating the real food without synthetic chemicals and preservatives. Intermittent fasting is famous for lowering the abdominal fats and extra fatty deposits of the body. This thing allows hormones to work efficiently. Intermittent fasting helps to gain lean body mass by producing growth hormone during fasting state. This phenomenon helps in the breakdown of adipose tissue and promotes ketosis. The body uses the fat tissue as energy sources and results in improved lipid profile with permanent weight reduction.

Keywords Intermittent fasting · Circadian rhythms · Weight loss · Fasting state

What Is Intermittent Fasting?

Intermittent fasting is change in eating pattern with time and caloric restrictions. IF is specific to a period based on fasting and feasting with time limitations [1]. Fasting persistently holds imperative part in almost every society from spiritual to medicinal outcomes. Human population normally consumes 3–4 meals per day, while the

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lab animals take food only when they feel hungry. This kind of overeating or continuous eating through meals with snacks in-between comes with outcomes like metabolic errors. Metabolic problems may include insulin imbalance/resistance resulting in other hormonal imbalances as well as abdominal adiposity. These problems originate with modernization and sedentary lifestyle. The combination of physical inactivity with eating all the time results in the deadly ailments not only body but also affects the brain.

Periodic fasting is the type of intermittent fasting in which time limit is defined from 16 to 48 h with very low caloric food. This may start from 2 days up to 21 or more days for proper results. Both intermittent fasting and periodic fasting showed a positive and curative impact on lots of metabolic issues. Intermittent fasting is an effective way for the improvement of metabolism by normalizing insulin levels and encourages faster weight loss.

Intermittent Fasting Schedules

Fasting is a well-known practice among the followers of different religions. The most attractive patterns of intermittent fasting are time-restricted feeding. There are several types of fasting mechanisms (Fig. 26.1).

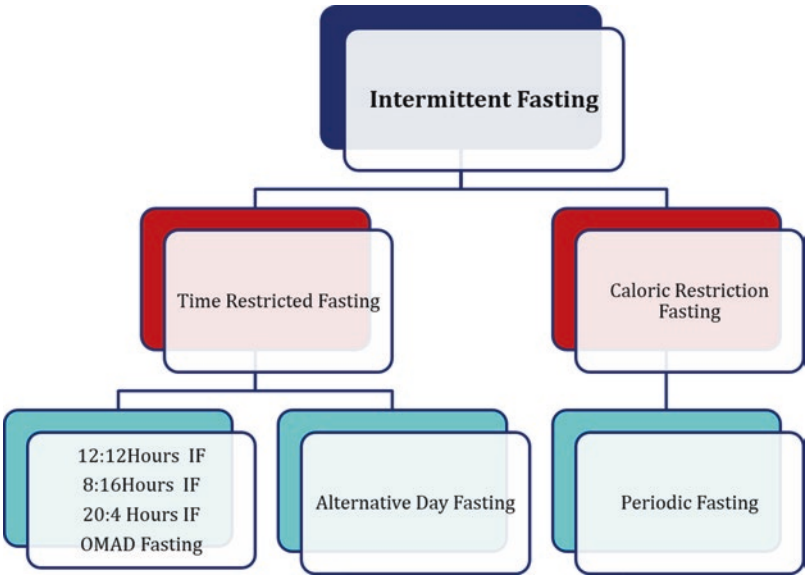

Fig. 26.1 Different techniques of intermittent fasting

12-Hour Fasting

Interruption of the circadian rhythm is strongly related to adiposity. The 12-h fast helps to maintain the nature's demand of eating only during the day and prohibited during night. Different studies revealed the secretes of reducing fat weight with 12-h abstinence of food following the circadian cycle. This method of fasting is easiest among all other techniques of fasting and requires division of 24 h into 2 equal parts. The 12 h during the day is a period of feasting, while during night the period is fasting. It is also called reverse fasting because it uses the power of circadian rhythms [2].

16:8 Intermittent Fasting

The most popular method used for weight loss is based on only 8-h period for eating during the day. Remaining 16 h the body breaks down the stored fats and glycogen reserves for energy requirements. High fiber and low caloric beverages including alkaline water are encouraged to be consumed during feasting intervals. This method suits with the busy routine of people and they get all the benefits including weight reduction and save time on eating which suits them [3].

The Warrior Diet 20:4

This time-restricted feeding pattern is very similar to ancient people who consume only some time and do not eat at all during the day. This method requires to eat totally unprocessed food during 4 h and to not consume anything in the remaining 20 h. That is why it is also known as the warrior diet.

OMAD (One-Meal-a-Day) 23:1

OMAD or single meal during 24 h holds a lot of health benefits. But this kind of fast diet pattern is advised only once or twice during the whole week. This technique of abstaining calories attained popularity after the book "eat-stop-eat" by Brad Pilon [4]. Studies also revealed that the single meal per 24 h has less benefits for weight related goals instead of small meals throughout the defined time-restricted fasting [3].

Periodic Fasting

This eating pattern involves fast for one or two alternative days in a week. This pattern involves reduced caloric intake for 2 days and consuming normally for other days (Fig. 26.2). This diet was promoted with the name of "the fast diet" [5].

Beverages Allowed During Fasting

The low caloric drinks are allowed during all king of time-restricted fasting patterns. They include water, green teas, herbal teas, tea, coffee, lemon water, alkaline, and detox water [4].

Alternate Day Fasting

The method involves no caloric consumption one day with alternative eating days [4].

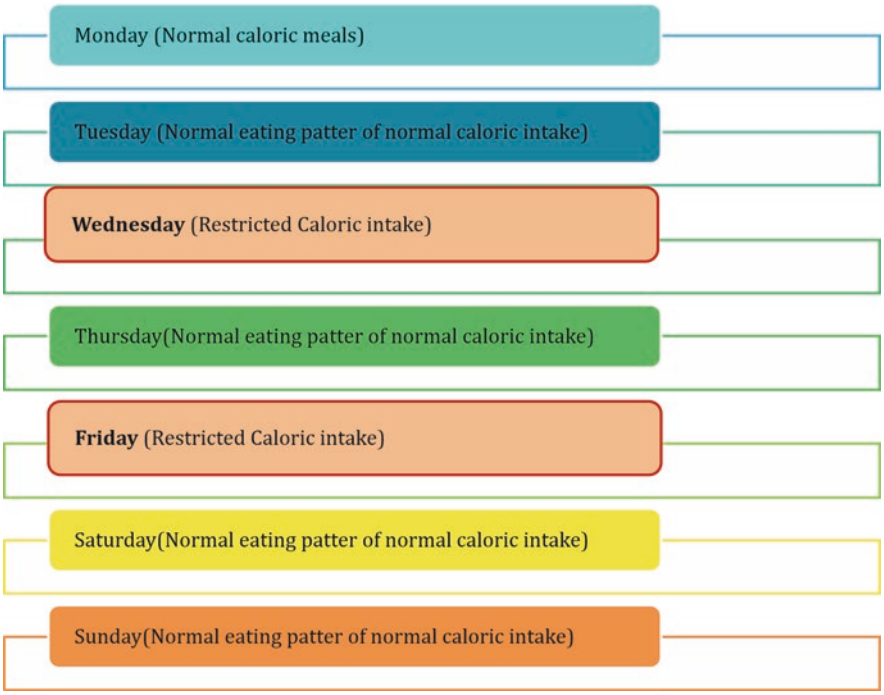

Fig. 26.2 The intermittent fasting 5:2 method

Modified Alternate Day Fasting

Every Other Day Diet

Modified fasting is actually not a complete fast diet. It allows 500 kcal consumption on the fast day [6].

Extended Fasts

Extended fasts are fasts lasting longer than one day. According to the book, The Complete Guide to Fasting, the real benefits of prolonged fasts including weight loss and reduced insulin levels are attained only by this method [7].

Instinctive Intermittent Fasting

This technique is totally based on the innate feeling of the body. A person eats only when feels hungry. According to this pattern a person can eat and skip food only by listening to the body instinct (Fig. 26.3) [8].

Nutrients Selection for Intermittent Fasting

A detailed description for the selection of nutrients for intermittent fasting has been mentioned in Table 26.1.

Fascinating Power of Intermittent Fasting

Fasting has a magnificent impact on the body from reducing weight to memory boosting and improved mental health (Fig. 26.4). Clinical evidence also provoked these huge health benefits come from doing intermittent fasting on animals. These feeding practices also reduce the burden of non-communicable and age-related diseases such as malignancies, mental issues, and heart diseases. Different research works reveal the time related fasting (TRF) among normal as well as obese population has enhanced health markers.

Different types of intermittent fasting	Duration/Mechanism of fasting	Descriptions
Time restricted feeding		• Simple fast for some time • Normally 12 to 16 hours a day
Alternative day fasting		• Cycle fast on every other day • 1 day fasting with 1 day feasting cycle
5:2 Intermittent Fasting		• Fasting for 2 days •Normal eating during 5 remaining days
The warrior Diet		• One Meal a Day •19-21 hours fast daily
Periodic Fasting		• 2 to 3 days Fasting • Caloric reduction up to 50% • Used for few times a year

Fig. 26.3 Different types of intermittent fasting

Cellular and Molecular Mechanisms of Fasting

1. Activation of adaptive cellular stress response signaling pathways that enhance mitochondrial health
2. DNA rehabilitation and autophagy
3. Periodic fasting also supports stem cell-based transformation
4. Averting and handling main aging disorders
5. Enhanced cellular stress resistance [11]

Cellular and molecular benefits of intermittent fasting have a positive impact on blood vessels, brain and cardiac cells which results in extended life span (Fig. 26.5) [12].

Mechanism of Fasting

When fasting, the body is allowed to cleanse itself and reach its optimal function levels (Fig. 26.6).

Table 26.1 Nutrients selection for intermittent fasting

Nutrients	Requirements	Type and sources	Not allowed
Carbohydrates [9]	55–65%	High fiber •Whole grains Sweet potatoes •Beetroots •Berries •Quinoa avocado •Carrot •Oats •Brown rice •Apples •Bananas •Mangoes •Kidney beans •Pears •Broccoli •Brussels sprouts •Almonds •Chia seeds •Chickpeas	•Refined sugars •High fructose corn syrups •Candies •Alcohol
Proteins	0.8 g/kg body weight	•Lean protein •Supplemental proteins like organ meat Seeds and nuts Beans and legumes Poultry and fish Eggs Dairy products such as milk, yogurt, and cheese Soy Seafood	Fried form of meat Highly processed and preserved meat
Fats	27–35%	Plant based oils Seeds Nuts Olive oil Avocado	Synthetic ghee Saturated fats Artificial butter
Mineral	According to RDA	Vegetable as salad	Large doses from synthetic sources
Vitamins	According to RDA	Fruits Whole form of fruits [9]	Artificial sources [10]

Circadian Rhythm

The human body has its own clock. The body achieves normal physiological functions on its maximum capacity according to this clock. Our behaviors throughout the day are also affected by rhythms of this biological clock. The gut behavior is involved in various metabolic and physiological functions of the body. And the gut functions directly depend on the circadian rhythms. Any interference of this rhythm can commence sequences of variations in metabolism proceeding to adiposity,

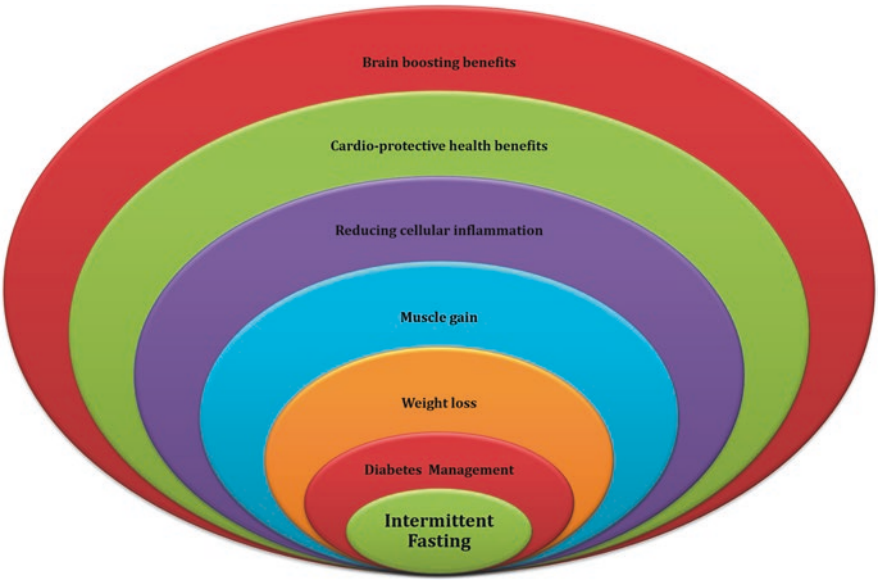

Fig. 26.4 Fascinating benefits of intermittent fasting

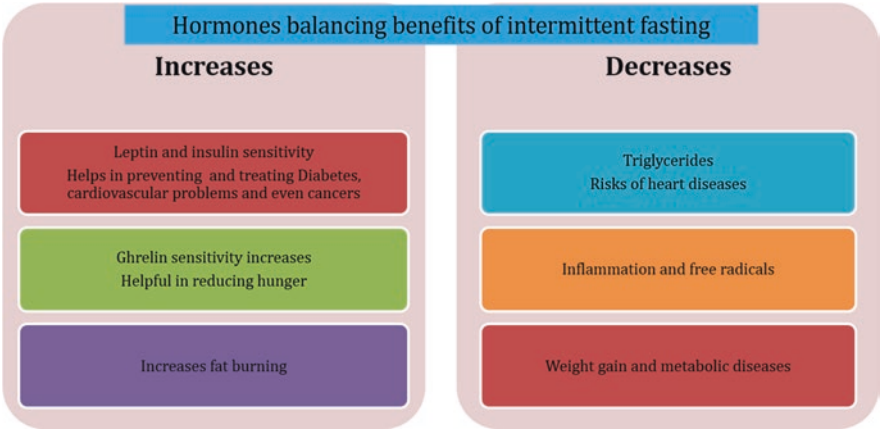

Fig. 26.5 Hormone balancing and disease preventing benefits of intermittent fasting

diabetes mellitus, tumors, and cardiovascular ailments. Intermittent fasting can protect and maintain these normal biological rhythms. Feeding signal are the important indicators in preserving these circadian rhythms. Different studies showed the 14-h overnight fasting improved body energy with additional benefits of better sleep and weight reduction [13].

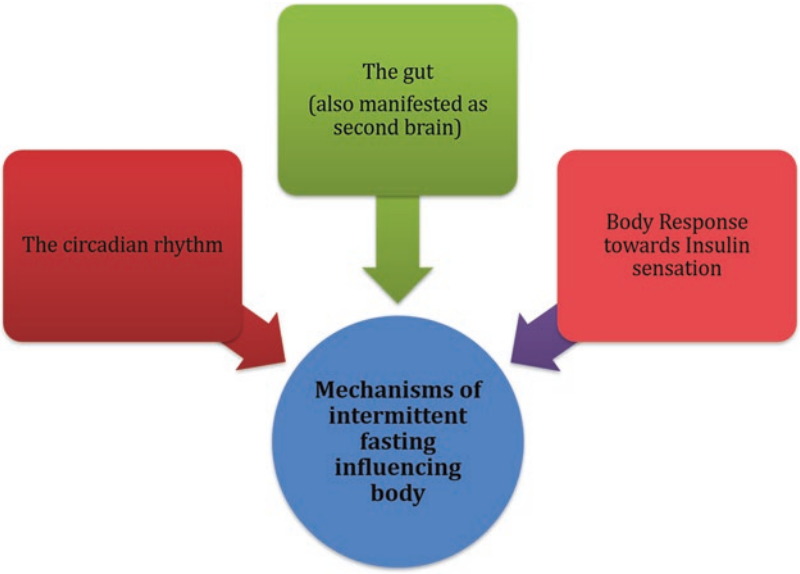

Fig. 26.6 Mechanisms of intermittent fasting influencing body

Gut Microbiota

Intermittent fasting has a positive effect on human microbiome. The gut microbiome is also considered as a second brain. The gut bacteria have the ability to memorize the response of food every time and play an important role in cognition, improving mood, reduce dementia and brain fog, and enhances mental clarity. Fasting actually gives time for rest to gut. Human gut does a very difficult task of extract nutrients and expel the waste from food. This function requires a lot of blood and continuous supply of oxygen. The person who is eating all the time can experience gastric issues by not allowing the repairing time to gut. Intermittent fasting precisely diminishes gut permeability and heals leaky gut syndrome [14]. This process reduces systematic inflammation and enhances gut overall integrity [14].

Insulin Sensitivity

The enviable impact of intermittent fasting improves insulin sensitivity, which further has countless benefits. Insulin is a peptide-based hormone and mainly performs anabolic functions. The most important function is to manage and absorb glucose from bloodstream into body cells.

Hyperinsulinemia

Hyperinsulinemia is a condition in which pancreas produces more insulin than normal. It happens due to decreased sensitivity of body toward insulin. This condition is known as insulin resistance.

Symptoms of Insulin Resistance

- Fatigue
- Increase in abdominal adiposity
- Dark skin patches (acanthosis nigricans)
- Impaired fasting blood sugar
- Pimples
- Polycystic ovarian syndrome (PCOS)
- Fatty liver disease
- Sugar cravings
- Hunger pangs
- Scalp hair loss in women
- High blood pressure
- Fluid retention
- High blood pressure
- Lack of concentration [15]

When muscle cells become more reluctant toward glucose absorption due to insulin resistance, the blood glucose level starts to rise from normal ranges. A series of metabolic malfunctions begins with the extra production of insulin. Pancreas produces insulin in response to sugar produced by food taken by a person. When people eat all the time continuously the pancreas produces insulin to compensate the glucose from the bloodstream. But when someone don't stop to eat years after years the pancreas may reduce the ability because it became reluctant or loses the ability to produce that much amount of insulin during 24 h. This thing eventually leads toward increased inflammation and impaired glucose [16]. Insulin resistance mainly causes these metabolic diseases directly (Fig. 26.7):

1. Metabolic syndrome
2. Diabetes mellitus
3. Polycystic ovarian syndrome (PCOS)
4. Cardiovascular disease
5. Nonalcoholic fatty liver

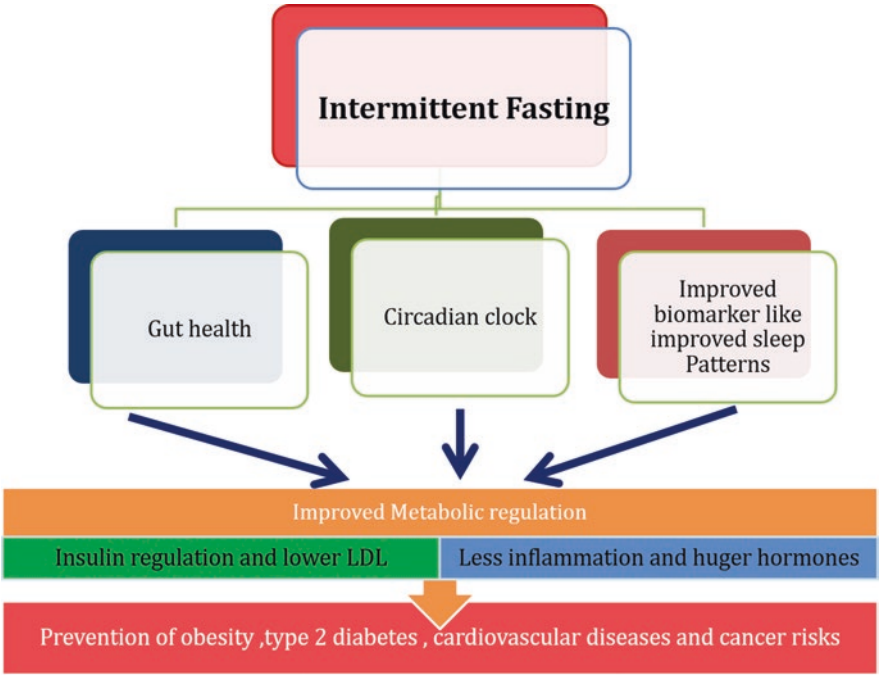

Fig. 26.7 Mechanisms of fasting in preventing metabolic and hormonal diseases

Intermittent Fasting as Treatment of Insulin Resistance

Intermittent fasting reduces the higher spikes of insulin. In the absence of insulin the body starts to consume its stored fat as energy and thus results in weight reduction [17]. The improved insulin sensitivity also regulates blood sugar by improving the sensibility of body tissue and cells [12]. The therapeutic fasting has the ability to reverse insulin resistance and stoppage of insulin therapy for maintaining blood sugar spikes. The patients become able in significant reduction of their fat weight and waist measurement. Improved control of HbA1c is also the privileged outcome of therapeutic fasting [1].

Health Benefits of Restricted Caloric Intermittent Fasting for Controlling Diabetes Mellitus

Diabetes is epidemic since the last two decades. It has a strong association with obesity especially with central adiposity. The diabetes is linked with further macro- and microvascular complexities. All these events lead toward a huge economic burden [1]. Researches manifested diabetes remission and maintenance with tight

caloric restriction which is ~840 calories/day and weight loss in a non-insulin-dependent diabetic population. This caloric restriction results in great control without using any insulin and some patients were able to reverse the disease. Pharmacological and surgical interventions among diabetics are controlled with the help of supervised therapeutic fasting. These diabetics also have some additional health benefits:

1. Insulin sensitivity is expanded
2. BP is normalized
3. Cellular oxidative stress is managed
4. Reduction in inflammation
5. Cellular stress resistance is improved

Animal studies demonstrate the reduction in caloric intake results in extended life span. The decreased meal frequency is associated with improved human health [12].

Intermittent Fasting for Reducing Obesity

Fasting is an adorable, natural, and powerful strategy for managing body weight. The body can consume glucose and ketone bodies for energy. But the body consumes ketone only in the absence of glucose. The continuous supply of glucose is the main reason for the limited use of glycogen and fatty acids for energy [11]. When a person stops eating during fasting phase, the insulin levels drop which allows the body for signaling the liver to consume glycogen and stored fats for energy production. The fat mobilization starts and they are converted into ketone bodies which are easily consumed by the brain and muscle tissues. The body normally cannot utilize both fuels (fats and sugars). Therapeutic fasting allows the body to relay on fat for fuel rather than only sugars. Fasting is a simple but significant method to maintain hormones for better metabolism and results in a reduction in water retention and fat weight [18]. The most famous among all fasting techniques is the alternative day fasting [19]. These routines convert the white fatty tissues into brown fat. Brown fats are metabolically more active fat and generate more energy. Fasting dramatically reduces fatty liver disease and ameliorates insulin resistance [20].

Limitations of Intermittent Fasting

Intermittent fasting has tons of benefits but it is not applicable to everyone. Some vulnerable groups require more calories for nourishment and growth. This nutritional advice is allowed only under complete observation of health care professional. The following individuals cannot participate in fasting:

- Diabetics—particularly those on insulin [21]
- Lactating women [22]
- Pregnant women [23]
- Individuals with a history of eating disorders [24]
- Children under the age of 18 [25, 26]

Conclusion

Intermittent fasting improves hormonal health biomarkers by normalizing hormonal imbalance. Moreover, it helps in improved body response toward insulin resistance, thus helps lowering the risk of diabetes and inflammations. IF becomes a proficient, easy, economical, and reliable procedure to diminish the insulin and glucose spikes, reducing extra belly fat, low risk of PCOS, and balancing other body hormones. IF is not recommended to some vulnerable groups including pregnant and lactating woman, growing kids, and patients of chronic diseases.

Conflict of Interest Nothing to declare.

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Chapter 27
Herbs and Spices as Natural Medicine for Treatment of Metabolic Disorders

Nizwa Itrat

Abstract Endocrine disorders like diabetes, adrenal fatigue, hyper and hypothyroidism, menstrual abnormalities, and sexual dysfunctions are growing day by day due to many environmental pollutants and endocrine disrupting chemicals coming from food and breakages. Hormonal imbalances can affect life of millions of people. Herbs and spices normalize the hormone in normal ranges. Hormones are key messengers for controlling almost all body systems. Hormonal imbalance is a troublous condition which has adverse effects on mood, appetite, metabolism, aging, and mental health. Adaptogenic herbs are unique healing herbs that promote hormonal balance, enhance immune functions, and reduce mental stress. These herbs eliminate toxins from the body and detoxify liver from harmful chemicals and endocrine disrupting chemicals. Herbal infusions and their essences have potential to cure hormonal disorders.

Keywords Medicinal plants · Hormones · Adaptogenic herbs · Herbal infusions Hormonal disorders

Introduction

The ductless hormonal system is known as *endocrine system* and it is the most sophisticated messaging system of the body. Basically, it is a collection of glands responsible to produce hormones for governance of body's metabolism, growth and development, tissue activities, sensual function, reproduction, attitude, and sleep. This assortment of glands is consisting of pituitary gland in the brain, thyroid gland in neck region, parathyroid glands adjacent to thyroid, adrenal glands on top of

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kidneys and pancreas near duodenum, ovaries (in females), and testicles (in males). Every gland produces specific hormone in the blood stream for special functions. Hormones produced by the gland travel through blood and detected by receptor site of the target cells or system. Sometime body's major organs mainly heart, kidneys, intestine, and liver also produce some hormones in some specific situations [1].

Categories of Endocrine Hormones

There are three main categories of hormones and their detailed description has been illustrated in Fig. 27.1. Different hormonal imbalances result in different diseases. Environmental toxic materials from food to air inhalation disturb normal hormonal production and their working. Phytochemical nutrients from herbs and spices were used from decades in treatment of these hormonal disturbances related to endocrine disturbing chemicals. These toxic materials cause a toxic body and those results in failure of messaging system of endocrine glands. These endocrine toxins mimic the original hormones and cause the deficiency or dominance of some hormones. There are different approaches for treatment of hormonal imbalance naturally. Among these diffident methods herbal extractions are important due to their significance. The most adorable treatment which was applied since centuries by midwives is herbal treatment (Fig. 27.2). Herbs were famous in correcting the disturbance of body hormonal system [1, 2]. The frequency of endocrine problems is rising day by day around the globe (Fig. 27.3). Many factors contributes in onset of hormonal

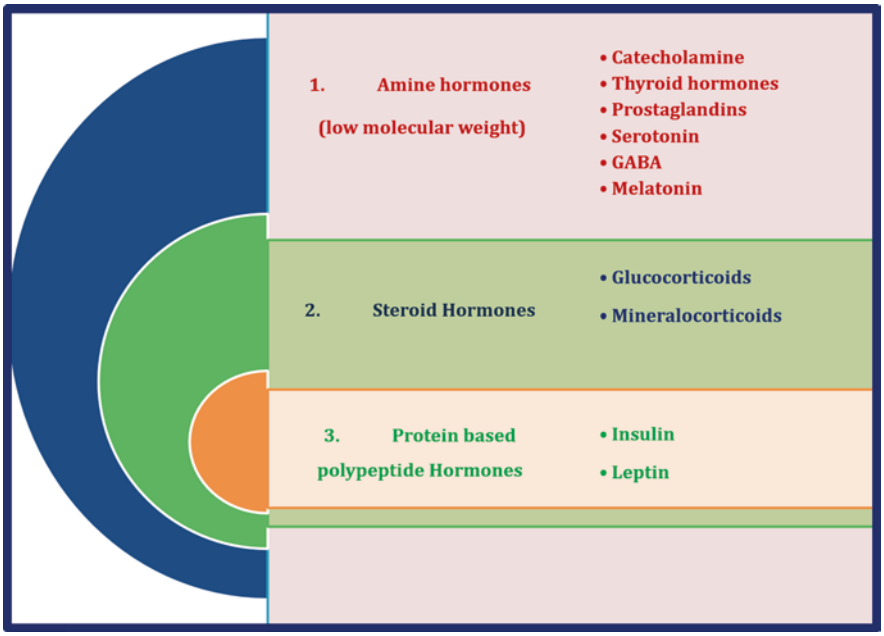


Fig. 27.1 Main categories of endocrine hormones

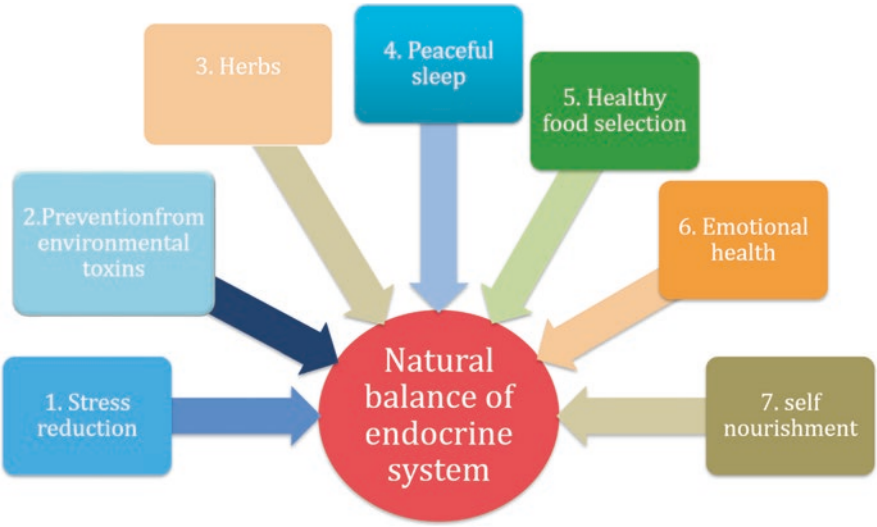


Fig. 27.2 Factor affecting on the natural balance of hormone system

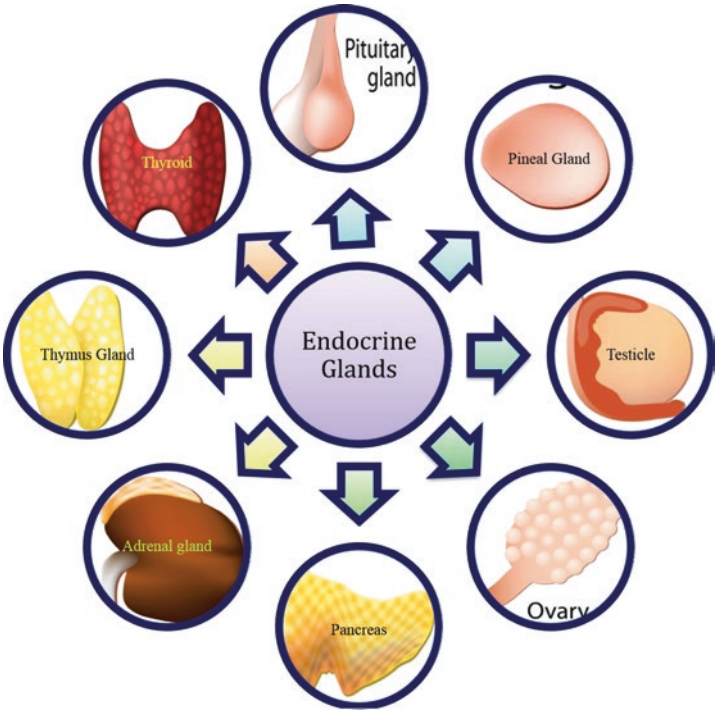


Fig. 27.3 Classical examples of endocrine glands

diseases like poor eating habits and air quality. Herbal treatment become the most popular and effective therapeutic one among all other options [3].

Herbs and Spices for Treatment of Pituitary Gland Disorders

The pituitary gland is smallest among all other but master of all endocrine glands. This is the important network association between the central nervous system and endocrine glands. Pituitary works under the influence of hypothalamus. The medical profile of different herbs can promote and also regain the normal function of pituitary glands function (Fig. 27.4).

Bladder Wrack

This herb is basically seaweed and an excellent source of dietary iodine. It has ability to treat the thyroid gland problems due to issue in pituitary gland compromised secretions. By healing the secretion of pituitary, it helps body in various ways:

Fig. 27.4 Classical examples of herbs that are used for pituitary gland health

- Improves digestion
- Slowed macular degeneration
- Better vision due to beta-carotene
- Enhances metabolism and weight reduction
- Reduces bad cholesterol from arteries
- Slow aging [4].

Kelp

Kelp is natural and nutritious source of iodine which increases the metabolism. It improves the metabolism and helps in losing weight. It is a natural diuretic herb which helps to get rid of toxin and extra water retention [5, 6].

Pau D'arco

This herb is known as natural hormone balancer especially sex hormones produced by pituitary. By doing versatile functions it also helps to modulate immune system and increase production of white blood cells [7, 8].

Nettle

This influential herb has ability to reverse iodine deficiency. It also improves kidney and thyroid glands functions [9].

Irish Moss

Irish moss distinguished for improved production of T3 and T4 and also known as plant thyroid [8].

Barberry Root

Barberry root facilitates in reversing hypothyroidism. It also enhances pituitary secretions to help normalizing thyroid and pancreas [8, 10].

Herbs and Spices for Treating Thyroid Gland Abnormalities

The thyroid gland resembles to butterfly in shape. It is located in lower front of neck. The thyroid gland secretes mainly two important hormones T3 and T4. These hormones control metabolism and perform various tasks like energy generation, temperature regulation and keeps vital organs function with synchronized [11]. There are wide variety of herbs for better thyroid functioning (Fig. 27.5). Normally three hormones are important for identification of thyroid gland function [12]. These are T3, T4, and calcitonin (Fig. 27.6).

Euthyroidism is normal working thyroid gland. Hyperthyroidism is over active thyroid secretion. Hypothyroidism is a condition in which thyroid gland not produce sufficient hormones required for body's metabolism [13]. The medical treatment of all thyroid conditions is based on pills and drugs based on hormone replacement formulas (Fig. 27.7). They have some side effects with their positive

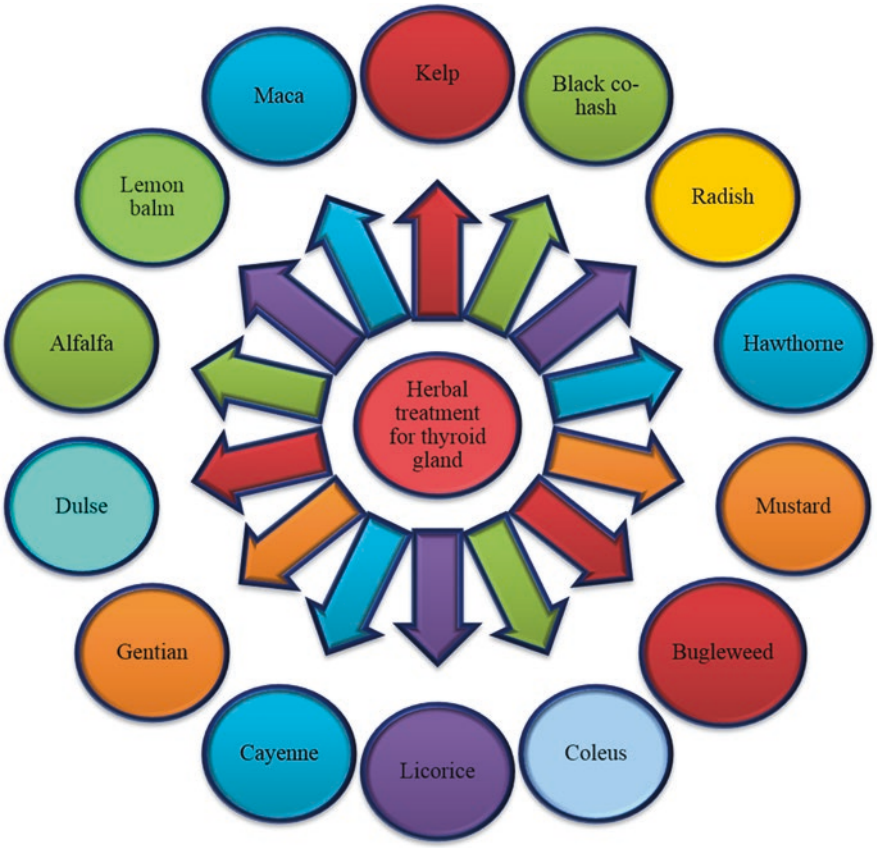


Fig. 27.5 Classical examples of herbal treatment for thyroid gland dysfunction

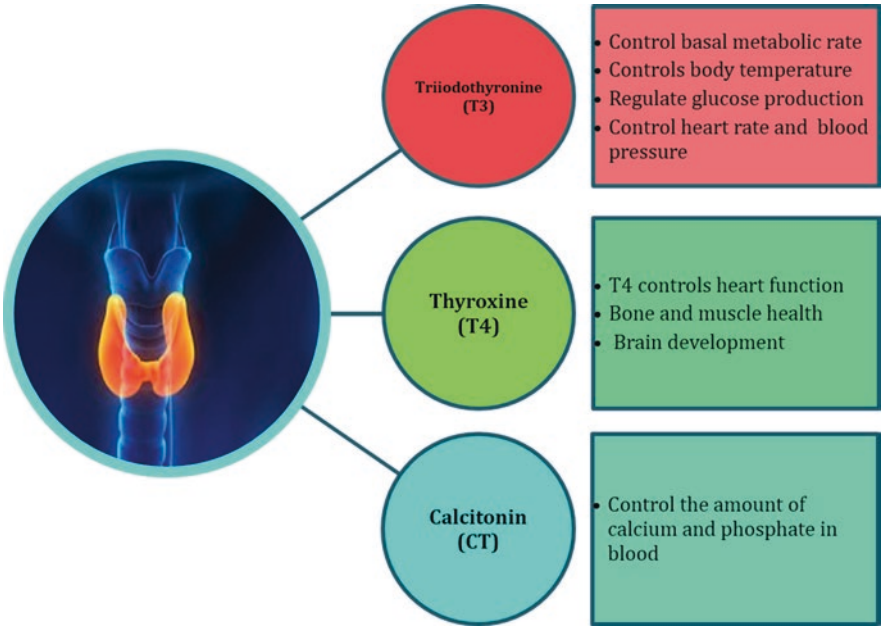


Fig. 27.6 Hormones produced by thyroid gland and their functions

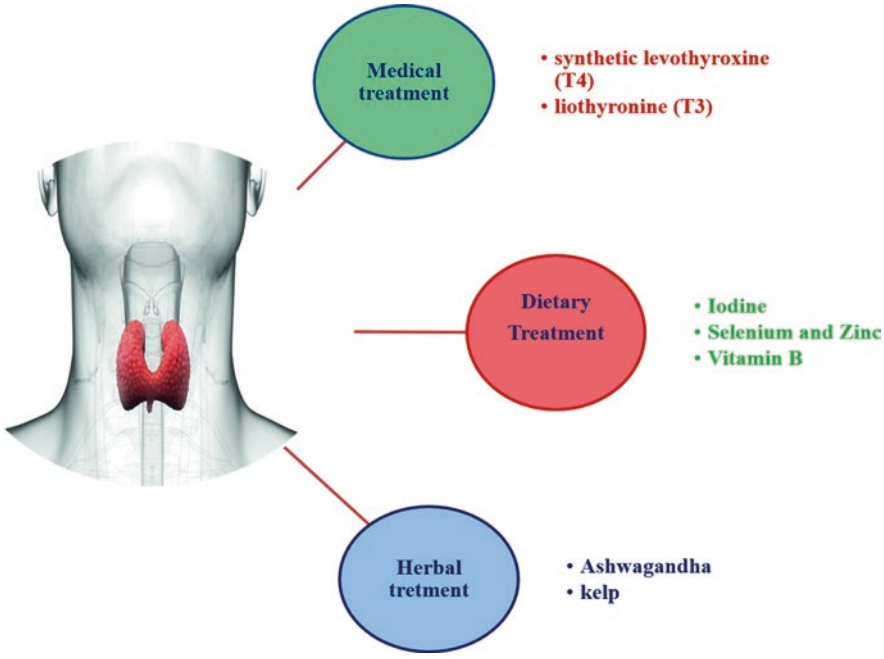


Fig. 27.7 Treatment options for thyroid problems

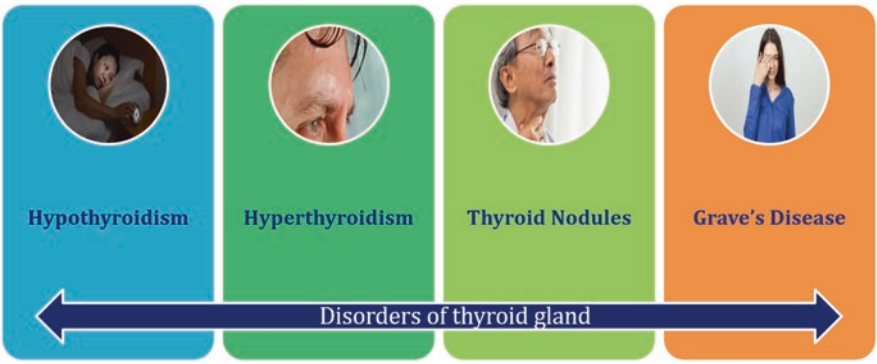


Fig. 27.8 Classical examples of disorder of thyroid glands

benefits. The herbalists emphasize the use of various herbs in the treatment of hypothyroidism without side effects and less expensive way (Fig. 27.8).

Therapeutic Strategies for Treatment of Thyroid Gland Dysfunction

Nutrients for Thyroid Gland

Classical examples of nutrients for the treatment of hypothyroidism have been illustrated in Fig. 27.9. The B-complex vitamins are important for patients suffering with low secretion of thyroid hormones. B_{12} is more important and found in various foods like milk, eggs, seeds, yogurt fish, and leafy green vegetables [14]. Selenium is very important mineral which works as anti-oxidant in the body ad protect thyroid gland from damages. It protects the gland against the enzyme thyroid peroxidase in hypothyroid patients. The important dietary sources for selenium include organ meat, tuna fish, beef, turkey, chicken, eggs, and mushrooms [15]. Zinc helps in conversion of hormone T4 to T3. Both selenium and zinc help to maintain the normal level of hormones in blood. Meat, legumes, nuts, and fish are considered as rich sources for zinc [16, 17]. Tyrosine is an important amino acid. Body requires tyrosine for production and conversion of thyroid hormones [18, 19]. Different researches proved that vitamin D deficiency is linked with hypothyroidism. Studies also proved that vitamin D supplements enhance the production of TSH levels in subjects with hypothyroidism [4]. Coconut oil may help with, little research but works for some, 1-2 tablespoons/day. Simple and processed foods make the thyroid function difficult and worse among hypothyroid patients. They increase the inflammation in the body which slows down the conversion from T4 to T3 [20–22]. Studies have also shown that some plants are also used for the treatment of thyroid dysfunction (Table 27.1).

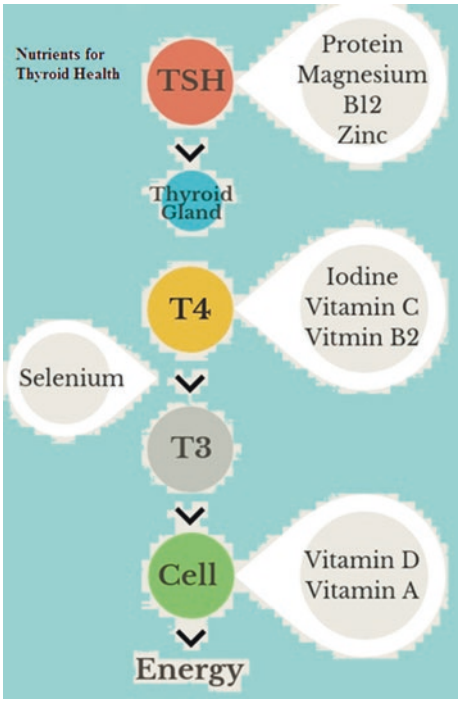


Fig. 27.9 Classical examples of nutrients for thyroid health

Withania Somnifera

Withania Somnifera is also known as white cherry or Indian ginseng. Ashwagandha is a saponin glycoside belongs to *Solanaceae* family. Moreover it improves thyroid functions due to its anti-oxidant properties [24]. Guggul helps to increase T3 production as well as promote the conversion of T4 to T3.

Bacopa

It boosts function of T4, not T3 also known as cognitive calming energy plants [25].

Rosmarinic Acid

It is an active component of many herbs including sage, Bugleweed, and Rose marry help in reduction rate of autoimmune disorders and also resists over function thyroid [26].

Table 27.1 Classical examples of herbs that are used for the treatment of thyroid dysfunction

Type of diseases	Name of plant (biological sources)	Chemical constituent	Uses	Image
Hypothyroidism [12, 23]	Gotu Kola (Centella asiatica)	Madecassic acid	Enhance synthesis of T4	
	Ashwagandha (Withania Somnifera)	Withaferin reduce oxidative stress	Improve thyroid activity, enhance antiperoxidation	
	Guggul (Commiphora mukul)	Guggulosterone	Thyroid stimulants in hypothyroidsm	
	Bladder wrack (Fucus vesiculosus)	Iodine	Goiter	

Type of diseases	Name of plant (biological sources)	Chemical constituent	Uses	Image
Hyperthyroidism	Lemon balm (Melissa officinalis)	Antioxidants	TSH suppressant	
	Rose marry (Rosmarinus officinalis)	Rosmarinic acid	Regulate thyroid hormones in normal range	
	Sage (Salvia officinalis)	Rosmarinic acid	Hormone suppressor	
	Motherwort (Leonurus cardiaca)	Rosmarinic acid	Thyroid hormone suppressant	

(continued)

Table 27.1 (continued)

Type of diseases	Name of plant (biological sources)	Chemical constituent	Uses	Image
	Gromwell (Lithospermum ruderale)	Qurectin	Anti-inflammatory activity	
	Bugleweed (Lycopus virginicus)	Rosmarinic acid Chlorogenic acid Lithospermic acid	Work for thyrosupressive agent	

Healing Herbs for Pancreas Gland-Related Disorders

Pancreas is unique vital organ composed of both exocrine and endocrine functions. It performs dual function of secreting hormones and enzymes [27]. The most important hormone released by pancreas is insulin for maintaining glucose in the normal range [28]. The glucose balance is important for health and diabetes is result of the misbalance of glucose (Fig. 27.10). The production of pancreatic hormones mainly insulin, gastrin, somatostatin, and glucagon is responsible for maintaining salt and sugar balance of the bodies. Islets of Langerhans are responsible for all endocrine function of pancreas [28, 29]. A detailed description of healing herbs for the treatment of pancreas gland-related disorder has been summarized in Table 27.2 and Fig. 27.11.

Obesity as Endocrine Disorder

Obesity is epidemic and related to increase incidence of metabolic syndrome. Due to less options of long-term weight reduction people are compelled to live with this adiposity. Energy homeostasis is most important thing for weight management. Recent studies proved that obesity is result of the failure of energy homeostasis due to endocrine disruption from environmental pollutants and lots of sources of EDC [47]. Annually 25 million deaths happened due to this disorder. Some synthetic formulas can treat obesity with low efficacy and lots of side effects. Herbs are best option in case of alternative option for the treatment of obesity. Currently

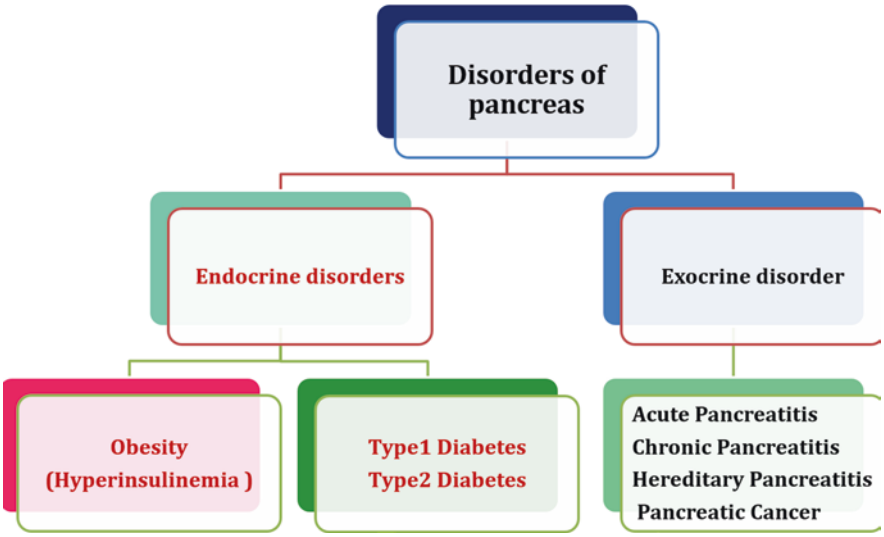


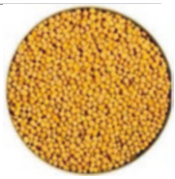
Fig. 27.10 Pancreas gland-related disorders

Table 27.2 Healing herbs for pancreas gland-related disorders

Common and scientific name of herb / spice	Preferred part and dose for therapeutic use	Mechanism of action	Benefits	Image of herb/ spice
Cinnamon (Cinnamomum zeylanicum and C. verum)	Bark of plant is used in powdered as well as in extract form	•Increases insulin production •Enhances sensitivity of insulin •Not significant effect inHbA1c but control FBS	Control Type 2 Diabetes The aqueous extract of C. verum bark enhances insulin sensitivity	
Cumin seeds (Black Cumin) (Cuminum cyminum) Bunium persicum Boiss	Extract, powder, and tea form [30]	•Flavonoids and phenolic contents enhance insulin production [30]	Anti-obesity properties of cumin increase insulin functioning Reduce glycemic level Reduce plasma glucose	
Curry leaves (Murraya koenigii)	Leaves can be used in both extract or powdered form 3 gm of curry leaves powder in human study 400 mg/kg in animal models [31]	•Helps in recovery of tissue injury due to diabetes	Improvement in blood glucose levels Reduce oxidative stress Good for Glomeruli and renal convoluted tubules	
Fenugreek (Trigonella foenum graecum)	Extract and powder forms are used [32]	Amino acid "4-hydroxyleucine" is active component	Improves glucose related insulin sensitivity Also helpful in normalizing LDL	
Garlic (Allium sativum)	Anti-obesity spice Fresh spice, dried powder, and extract forms are used	Contain sulfur containing amino acids Stimulate the production of insulin by beta cells [33]	Keeps glucose under control Also lowering cholesterol and has hypertensive properties	

(continued)

Table 27.2 (continued)

Common and scientific name of herb / spice	Preferred part and dose for therapeutic use	Mechanism of action	Benefits	Image of herb/ spice
Ginger (Zingiber officinale)	Raw ginger, 500 mg/kg Fresh spice Dried powder Ginger tea Extract form [34]	High in antioxidants Gingerol Hypolipidemic effect [35]	Reductions in fasting blood glucose Valuable increase in insulin level HbA1c levels	
Mustard (Brassica nigra)	Mustard seed sprout Seed Oil Powder Sauce form [36]	Allyl isothiocyanate is active component	Hypoglycemic effect Promotes glycogen synthetase activity Suppression of enzymes responsible for glucose formation	
Onion (Allium cepa)	Fresh as salad Used in cooking in lots of recipes	Sulfur containing amino acids S-methyl cysteine sulfoxide [37]	Activate insulin producing cells by pancreas	
Pippali (Piper nigrum and P. longum)	Used as spice in different foods	The active alkaloid called piperine [37, 38]	Reduce liver enzyme to produce more glucose and control diabetes	
Turmeric (Curcuma longa)	Powder form as spice extract form	Curcuminoids are strong antioxidants of turmeric Anti-diabetic power By increasing insulin production [39]	Maintain blood glucose Reduce oxidative stress Reduction in inflammation	
Aloe vera	Extract Gel form	Lignin, saponins, salicylic acids, and amino acids [40]	Good for pre-diabetics and diabetic due to its nutrients and soluble fiber	

(continued)

Table 27.2 (continued)

Common and scientific name of herb / spice	Preferred part and dose for therapeutic use	Mechanism of action	Benefits	Image of herb/ spice
Neem Azadirachta indica	Powder and tea forms	Cheap and efficient method of controlling diabetes [41]	Effective for diabetic foot ulcer treatment	
Horsetail equisetum arvense	Extract form	Reduces pancreas inflammation [42]	Helpful in regeneration of pancreas and maintain the blood sugar level	
Marigolds *calendula*	Oil is used	Anti-genotoxic and anti-inflammatory properties [43]	Used to treat diabetic foot ulcer topically	
Goldenseal Hydrastis canadensis	Wild herb	Helps in lowering blood sugar levels [44]	Increases insulin by β-cells in pancreas	
Licorice Root Glycyrrhiza glabra	Herb used in both powder and extract forms	Excellent for pancreas health [45]	Anti-inflammatory properties in case of pancreatitis	
Lemons Citrus limon	Whole part may be used Lemon extract	Helpful in releasing digestive enzymes from the pancreas [46]	Essential oils from peel have anti-diabetic effect	

people come back to treat diseases with natural ingredients like Cambodia hoodia, herbal tea, *Citrus aurantium*, fenugreek, white beans, yohimbine, chitosan, fitostreols, and guar gum [48, 49]. Excessive insulin secretion is contributing factor in obesity.

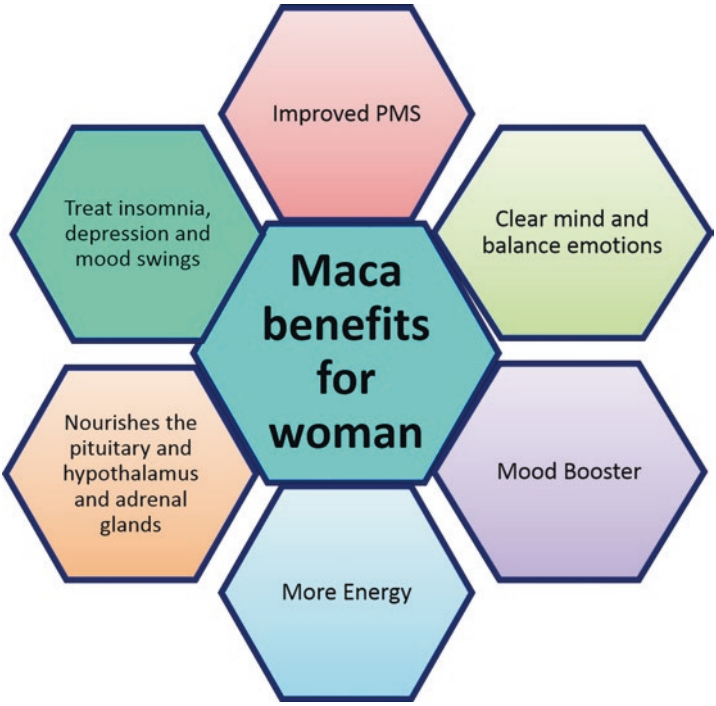


Fig. 27.11 Maca benefits for woman

Herbs and Spices for Weight Reduction

Herbs and spices gaining acclaimed in therapeutic treatment of obesity and related complexities without any serious side effect. The most common examples of herbs and spices that are extensively used for the weight loss have been summarized in Table 27.3.

Healing Herbs for Female Hormonal Problems

Maca

This marvelous herb is used from centuries for both male and female infertility treatment. Maca roots powder has potential to enhance fertility and correct hormonal imbalance. Basically, it is adaptogenic herb (it adapts to each body's circumstances and balances hormones depending on that person's needs). It regulates the hormones in normal range. If body is producing some extra amount of hormone, it reduces and suppresses the production and if body is deficient, then it helps to pro-

Table 27.3 Herbs and spices for the treatment of weight loss

Allium sativum common name: garlic	*Nelumbo nucifera common name: indian lotus*	*Elettaria cardamomum common name: cardamom*
Liver steatosis was ameliorated by intake of garlic is proven. Treat hypercholesterolemia [50]	Helps in reducing weight by inhibiting the alpha-amylase and lipase activity and regulating lipid metabolism Inhibited absorption of lipids and carbohydrates Accelerated lipid metabolism and up-regulated energy expenditure [51]	Cardamom powder intake ameliorated the fibrosis in liver It has ability to prevent dyslipidemia, oxidative stress, and hepatic tissue damage [52]
		
Cinnamomum verum common name: Cinnamon	*Camellia sinensis common name: Green tea*	*Taraxacum common name: Dandelion*
Affordable anti-diabetic and anti-obesity treatment Increase the body response to insulin Help in weight managemnt [53]	Most studied herb for weight loss But weight loss was not significant Small weight changes are seen in experimental trials and less effective in maintenance. It does not mean this herb is not for weight reduction. It is helpful but requires some long time for targeted weight loss [54]	Poweful therapy for non-alcholic fatty liver disease Its extract also inhibit fat accumulation in hepatic cells This also reduces insulin resistance [55]

		
Aloe barbadensis Common name: Aloe vera	*Syzygium aromaticum Common name: Cloves*	*Zingiber officinale Common name: Ginger*
Aloe vera has effect on liver enzymes that regulate cholesterol and fat Aloe sterol have fantastic potential to reduce metabolic syndrome and central adiposity [56, 57]	By increasing metabolic rate cloves are helpful for losing weight [58, 59]	Significant reduction in γ-glutamyl transferase, alanine aminotransferase, and inflammatory cytokines Therapeutical treatment of NAFLD [60, 61]
		

(continued)

Table 27.3 (continued)

Hoodia gordonii Common name: Kalahari cactus	*Murraya koenigii Common name: curry leaves*	*Foeniculum vulgare Common name: Fennel*
Hoodia gordonii suppresses the overall food intake Better water consumption Helpful to lose mean body mass gain and reduce fat easily [62]	Improve insulin sensitivity Enhanced energy cycle [63]	Boosts metabolism Improves digestion Removes toxins Helpful for weight reduction due to water retention [64]
		

duce more hormone [65]. A schematic representation of benefits of this herb has been illustrated in Fig. 27.14.

Red Raspberry Leaf

The benefits of red raspberry have been briefly summarized in Table 27.4.

Vitex

Vitex actually does not contain any actual hormones but it works to help naturally balance the body's hormones by regulating the pituitary which is "master glands" of the body. The pituitary sends messages to other glands to produce hormone. This communication between glands through hormone is called a hormonal feedback loop [67]. But if the pituitary gland is not balanced, then balance of the other glands will not be possible (Fig. 27.12).

Milk Thistle

Milk thistle is the most famous herb due to its countless health benefits. It is one of the most effective herbs for liver detoxification and balancing the extra number of hormones produced in the body. It can alleviate the estrogen dominance issue and also helpful in management of progesterone in normal range. Liver is the processing plant which removes toxins and hormones mimickers from the body and helpful in normalizing hormonal imbalance (Fig. 27.13). Oat straw (*Avena sativa*) reinforces the nerves, relaxes the body, sustains the blood, better moods, improves digestion, soothes the stomach, adjusts the endocrine system, and supports the bones and skeletal system due to high amount of bio-available minerals like calcium, magnesium, and silica. This incredible herb (Fig. 27.14) has also benefited to the hair, skin, and nails. It contains diuretic qualities and potential of reducing cholesterol and protecting heart health [68].

Herbs for Lactating Mothers

Nursing mothers require extra nutrients. Several herbs support optimal and healthy production of breast milk. Nursing mothers also require extra water intake for hydration. Any herbal tea to support lactation including Stinging Nettle, Goat's rue,

Table 27.4 Benefits of red raspberry

Rubus idaeus is used for making tea which is delicious and contains nutraceutical potential to treat female hormonal issues especially during labor. The leaves are nutrient dense and make this herb powerful tonic for female gender.	
	*Rubus idaeus* is fantastic herb with huge amount of almost all vitamins especially vitamin C and minerals.
Before pregnancyhormonal balancing benefits	
	1. Enhances fertility in both women and men 2. Decreases heavy blood flow 3. Provides relief during Painful menstrual cramps

Rubus idaeus Teafor hormonal balance during pregnancy	
1. Avert miscarriage rate during first trimester and control hemorrhages. 2. The uterine strengthening qualities of this herb make this female tonic for all hormonal issues 3. Calm during pregnancy related nausea 4. Reduce pain length during and after labor [66]	
After pregnancyhormonal balancing benefits	
Stimulates and enhances milk production during lactation period 	

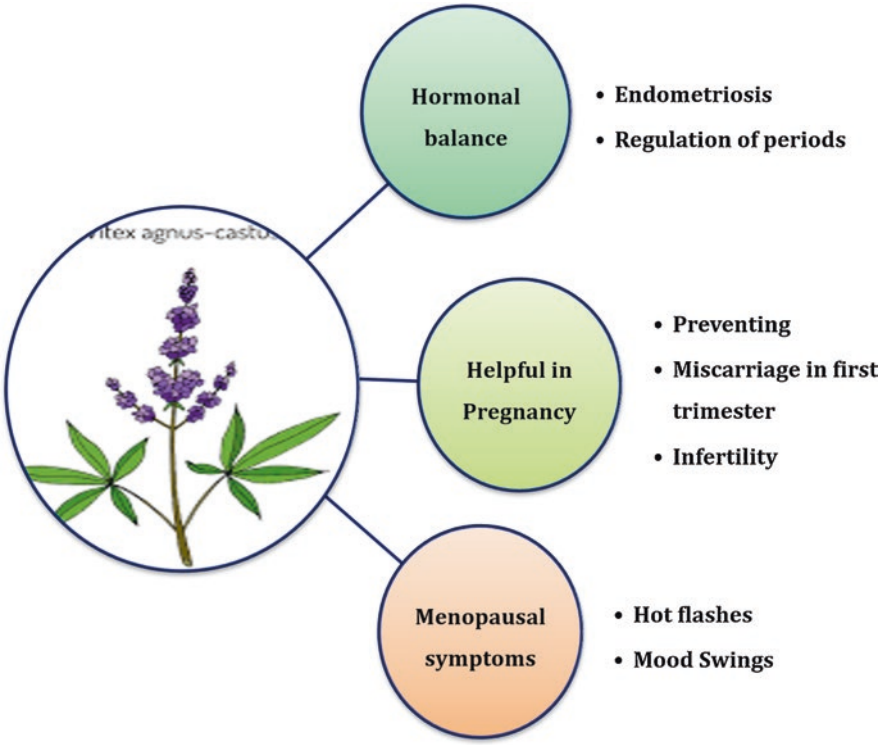


Fig. 27.12 Benefit of Vitex agnus for female hormones on different life stages

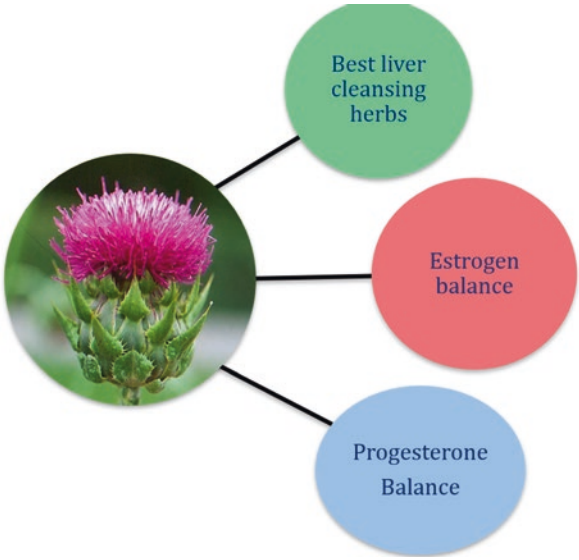


Fig. 27.13 Health benefits of milk thistle

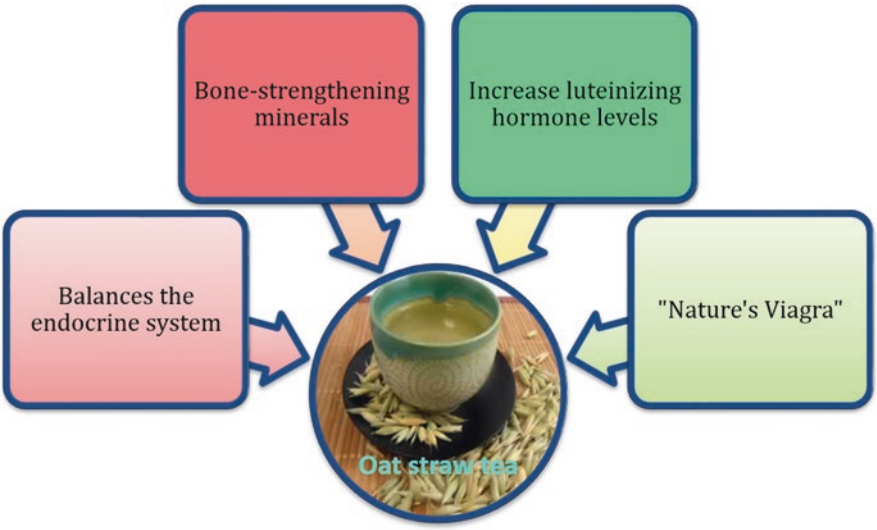


Fig. 27.14 Role of oat straw tea in hormonal balance

and fenugreek can be used. These herbs support hormones to maximize the milk production [68–70].

Herbs to Support Menopause Changes

Women face more hormonal changes throughout the life than man. By keeping the mind and body in a balance state through normalizing hormones is important to enjoy the life. When woman face menopause, the ovaries stop producing egg and estrogen. The progesterone production is also decreased [71]. Black Cohosh extracts and Vitex berry were used to support healthy transitions from menstruation to secession of periods [72].

Herbs and Spices for Male Hormones

Testosterone is an important male hormone. It is very important for male health and reproduction. A low production in testosterone is a result of exposure with a lot of chemicals from food, water, drug, pollution, and environment. Some estrogen mimicking chemicals also result in increased amount of estrogen in male gender. This will also alter the normal functioning of testosterone [73]. During aging process and metabolic diseases like diabetes also results in low testosterone production. Sleep deprivation severely affects the production of testosterone [74]. Low testosterone

results in several health problems and shows different symptoms. Overweight and obesity are associated with low testosterone. Weight management is achievable with the help of intermittent fasting and high intensity work outs [75]. A diet rich in nutrients is also important for male health. Strength training increases the lean body mass and improves hormones functions. Squats and other resistant trainings boost testosterone significantly [76]. Mineral like zinc is very important for testosterone. Only zinc deficiency is associated with low levels of testosterone [77]. Vitamin D is important for the sperm development. It is a steroid hormone which boost libido by increasing testosterone. Even among overweight males it improves testosterone to optimum level [78]. Stress badly affects all parts of body. It negatively affects the brain and hormones. Stress actually produces cortisol hormone which reduces the testosterone level [79]. High blood sugar in response to excessive intake of refined carbohydrates also results in low testosterone. High blood glucose triggers insulin in excessive amount which is the reason of low testosterone activity [80]. On the other hand, healthy dietary fats improve testosterone production [81]. Omega 3 fatty acids from walnuts and flaxseeds, omega 6 fatty acids from butter and organic milk are good options [82]. Branch chain amino acids are also considered good for naturally improving testosterone. Whey protein provides more amino acids and has more significant testosterone production along with resistant training [83].

Herbs and Spices for Balancing Testosterone

Herbs and spices are considered natural treatment of different ailments and hormonal problems. Nutraceutical compound from spices like ginger, cardamom, and garlic not only enhances taste of food but also provides anti-inflammatory and anti-carcinogenic properties [84].

Damiana Leaf

It is also known as *Turnera diffusa* plant. Its leaves contain bioactive components including fatty acids, glycosides, and caffeine. They improve the receptor cite of hormones [85].

Tongkat Ali

The extract from roots of tongkat ali herb is found a powerful aphrodisiac. It is found in Malaysia, Indonesia, and Thailand. It has equal benefits both for men and women in improving libido without any kind of side effects [86].

Horny Goat Weed

This is a famous Chinese herb used for boosting testosterone. It improves blood flow and beneficial for both genders [87].

Tribulus Terrestris

This is an ancient herb used from 400 years for healing properties. It overcomes the deficiency of low testosterone and promotes hormonal balance. The amazing health benefit of this herb is its ability of gaining muscles without weight lifting. It enhances the sex derive [88].

Rhodiola Rosea

Rhodiola Rosea is famous by another name Rosavin and "Golden Root." This herb is very important for losing weight and improving energy and brain functions. Basically this is adaptogen herb which means it is helpful for body to adapt chemical, physical, and environmental stress. It helps in combating low testosterone. Low testosterone creates adipose tissue formation around the abdomen. This herb reduces body fat and improves testosterone activity. It also improves sleep quality and reduces stress. It helps in formation of red blood cells and promotes good mood [89].

Maca

Maca is roots of Lepidium meyenii plant [90]. Oral administration of maca significantly improves spermatogenesis. It improves sexual behavior, sperm quality, and motility [91].

Moringa

Moringa is most nutritious and beneficial plant for both male and female health. Its nutrient contribution provides overall stamina and energy due to its protein and vitamin C content.

Conclusion

Herbs are nutritionally dense products from plant origin with tremendous properties on health. Herbs and some spices have excellent nutrients and antioxidants that can alleviate imbalance hormone issues. Herbal oils and infusions can cure and reduce hormone related carcinomas. Moreover, herbs can heal the problems related to imbalance hormones, i.e. mood swings, poor gut functions, and weight changings. They are easy, cheap, and harmless choice for treating these imbalances.

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Chapter 28
Bioactive Compounds for the Treatment of Metabolic Disorders

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Abstract The exposure of endocrine disrupting chemicals results in disruption of normal energy homeostasis control. Decrease metabolism of carbohydrates, proteins and fats occur due to EDCs induced thyroid dysfunction. The obesogenic and metabolic dysregulation ability leads to development of metabolic disorders. Plasticizers (bisphenol A), persistent organic pollutants (dioxins), organotins (tributyltin), and organochlorines (dichlorodiphenyltrichloroethane) are examples of some EDCs. There has been an increasing focus to investigate association between human exposure to EDCs and disease over the past few decades. Bioactive compounds are found to be effective in these EDCs induced metabolic disorders including diabetes mellitus, hypertension, obesity, hyperlipidemia, and non-alcoholic fatty liver disease. These compounds obtained from fruits, vegetables, and whole grains exert pharmacological effects in humans and play important role in defense and signaling. The use of these compounds is advantageous due to easy availability, safety, and few side effects. The different therapeutic activities of medicinal plants (antioxidants, antiinflammatory, anti-carcinogenic, antimicrobial, anti-malarial, anticholinergic, hypoglycemic, anti-leprosy, and antidiabetic) are basically attributed to the bioactive principles. Polyphenols, phytosterols, carotenoids, prebiotics, vitamins, and flavonoids are effectively used in treating EDCs induced diabetes mellitus, hypertension obesity, hyperlipidemia, and non-alcoholic fatty liver disease.

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Introduction

Bioactive compounds are non-nutritional substances that are found in food or dietary supplements and are responsible for changes in health status of living organisms [1, 2]. The impact of these changes can be positive or negative and depends on respective bioactive substance, its dose, bioavailability, and concentration in specific cells, tissues, or whole body [3]. These compounds are typically produced as secondary metabolites that play an important role in defense and signaling [4]. Therefore, these secondary metabolites exert pharmacological effects in humans [5].

Phytomedicines are becoming increasingly popular for their therapeutic responses as an alternative to synthetic medicines [6]. They are more acceptable due to several advantages including fewer side effects, ease in availability, and cost-effectiveness. The different therapeutic activities of medicinal plants (antioxidants, anti-inflammatory, anti-carcinogenic, antimicrobial, anti-malarial, anticholinergic, hypoglycemic, anti-leprosy, and antidiabetic) are attributed to the bioactive principles [7].

Antioxidants, carotenoids, essential oil, and flavors are bioactive compounds that are incorporated in food products. These compounds not only develop nutritional and health properties but also enhance sensory characteristics and are responsible to modulate metabolic processes in human body [8].Currently, there are no recommended daily intake values of bioactive compounds. Since these compounds are distinct from nutrients and have effect on human health, therefore, it is necessary to establish safe recommended daily intake [9].

Source of Bioactive Compounds

Fruits, vegetables, and whole grains are major sources of bioactive compounds [10]. These sources include an extremely heterogeneous class of bioactive compounds (phytosterols, organosulfur compounds, carotenoids, tocopherols) in different concentrations [11]. However, bioactive compounds are not only confined to plants. They are also obtained from other living organisms and microorganisms producing useful secondary metabolites [12].

Classification of Bioactive Compounds

Bioactive compounds are classified based upon their chemical structure. Carotenoids, phenolics, alkaloids, nitrogen containing compounds, and organosulfur are primary classes of these compounds. However, these classes are further stratified into subcategories (Fig. 28.1) [13].

Endocrine Disrupting Chemicals Induced Metabolic Disorders

Endocrine disrupting chemicals (EDCs) are substances in the environment (air, soil, or water supply), food sources, personal care products, and manufactured products that interfere with the normal function of your body's endocrine system. There has been an increasing focus to investigate association between human exposure to EDCs and disease over the past few decades [14]. Special attention is given

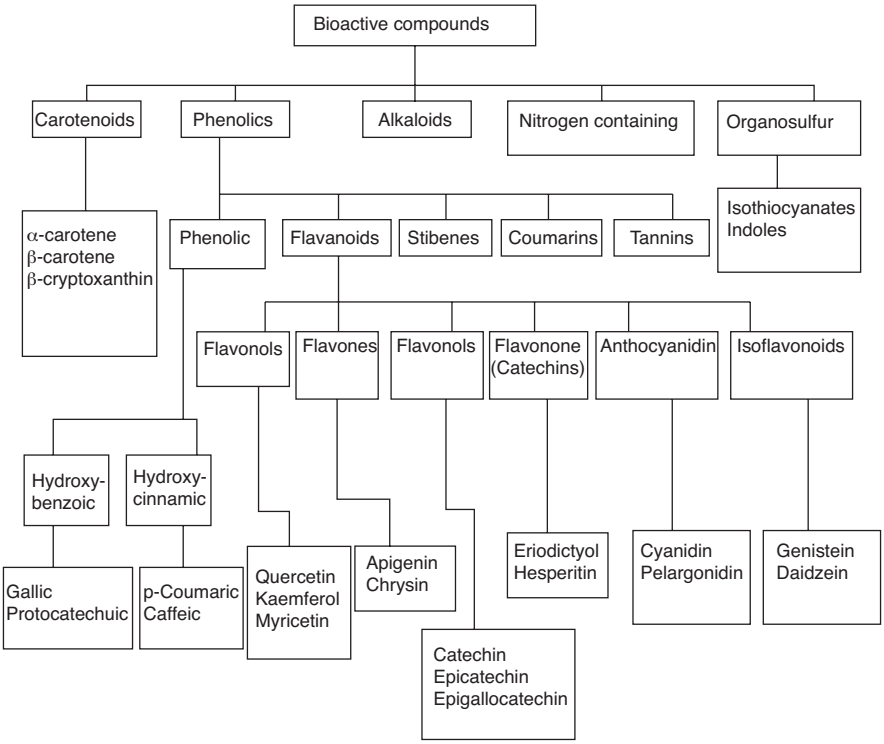

Fig. 28.1 Classification of bioactive compounds (figure is self-constructed and data is extracted from Maharaj 2015) [13]

to man-made organic pollutants, persistent organic pollutant (POPs) [15]. POPs are easily accumulated in fatty tissues due to their lipophilic nature [16]. Therefore, the exposure of these endocrine disrupting chemicals results in disruption of normal energy homeostasis control [17]. Thyroid function become impaired and result in decrease metabolism of carbohydrates, lipids and proteins [18, 19]. Hence, the obesogenic and metabolic dysregulation ability leads to development of metabolic disorders. In this chapter we have discussed the effect of bioactive compounds in these EDCs induced metabolic disorders including diabetes mellitus, hypertension, obesity, hyperlipidemia, and non-alcoholic fatty liver disease.

Bioactive Compounds and EDCs Induced Type 2 Diabetes Mellitus

Insulin insufficiency or insulin dysfunction leads to metabolic disorder characterized by Diabetes [20]. EDCs such as bisphenol A act on non-classical estrogen triggered pathways leading to metabolic dysfunction and disruption of insulin signaling and glucose metabolism resulting in diabetes mellitus [21–23].

Effects of Bioactive Compounds in Combating Type 2 Diabetes Mellitus

Bioactive compounds have been proposed to reduce the incidence and progression of many diseases including T2DM. The use of these compounds is advantageous due to easy availability, safety, and few side effects [24, 25]. Polyphenols, phytosterols, carotenoids, and prebiotics are major bioactive compounds that have been shown promising activity type 2 DM.

Resveratrol

Resveratrol exhibits antioxidant and antiinflammatory properties, maintains metal homeostasis, and increases mitochondrial function. The actual source of resveratrol is red wines, grapes skin and seeds [26]. Resveratrol potentiates glucose-stimulated insulin secretion and glucose metabolism in insulin secreting cells [27].

Quercetin

Quercetin is a flavonoid that has the potential for the treatment of DM [28–30]. Quercetin is found in broccoli, apple, tea, and red onions and exhibits antioxidant, antiapoptotic, and antiinflammatory properties [31]. It regulates phosphorylation of

extracellular signal regulated kinase (ERK1/2) and potentiates glucose-induced insulin secretion and protected β-cell function [30].

Genistein

An isoflavone found in variety of plants like soybeans, fava beans, and chickpeas and exhibits health benefits [32, 33]. Dietary supplementation of genistein improves glucose tolerance, increases β-cell mass, and reduces apoptosis [34].

Hesperidin

Hesperidin possesses beneficial effects for treatment of T2DM. It is found in citrus fruits such as oranges and lemons. Hesperidin increases serum insulin and decreases glucose and HbA1c, vitamin C, and vitamin E [35]. Hesperidin has antiinflammatory, antioxidant, and antidepressant properties [36–38].

Rutin

Rutin is a flavonoid that also possesses antioxidant, antihyperglycemic, and neuroprotective properties. Vegetables and fruits including figs, buckwheat, asparagus and apples are rich source of flavanoids [39–41]. Rutin improves oxidative stress, decreases serum glucose, and decreases serum lipids [42].

Carotenoid

Lycopene is a carotenoid that exhibits antidiabetic effect. The source of lycopene is pink grapefruit and tomatoes. Lycopene decreases lipid peroxidation and increases activity of antioxidant enzymes which in turn increase insulin level, decrease glucose levels, and improve serum lipids profiles [43–46]. Lycopene provides protection to kidneys against diabetes mellitus induced morphologic destructions [47]. Therefore, lycopene has the property to improve vascular complications associated with T2DM.

Vitamins

Vitamin A is effective for treatment of T2DM because it regenerates β cells and increases insulin sensitivity [48]. Vitamin D reduces risk of T2DM by modulating β cell function. It also increases insulin sensitivity and reduces inflammation [43].Vitamin E has been considered to improve activities of antioxidant enzymes such as glutathione reductase, catalase, and glutathione peroxidase and hence signifi-

cantly reduce glucose level [49]. Table 28.1 describes the summary of sources, proposed mechanisms of action, and therapeutic properties of various bioactive compounds used in DM.

Effect of Bioactive Compounds Against Hypertension

Hypertension is classically defined as blood pressure measurement exceeding a threshold of 120/80 mm Hg. Impact of endocrine disrupting chemicals on hypertension is evident by various studies. Higher systolic BP in childhood and adolescent was associated with exposure to phthalates [50]. In children, higher blood pressure is also observed due to increased exposure to pesticides [51]. The possible cause of association between EDCs and hypertension may involve increased oxidative stress and proinflammatory response [52]. Phthalates may activate peroxisome-proliferator activated receptor (PPAR) by acting as an antagonist on thyroid hormone, cortisol, and androgens [53]. Epigenetic changes are considered as another potential cause of EDCs induced hypertension [54].

Table 28.1 Bioactive compounds against EDC's induced diabetes mellitus

Sr.#	Bioactive compounds	Source	Mechanism of action	Therapeutic property
1	Resveratrol	• Red wines • Grapes skin • Seeds	• Glucose-stimulated insulin secretion • Improves insulin sensitivity • Lower hepatic glucose production	• Antioxidant • Antiinflammatory
2	Quercetin	• Broccoli • Apple • Tea • Red onions	• Increase glucose uptake via stimulation of GLUT4 translocation • Phosphorylation of extracellular signal regulated kinase(ERK 1/2) • Potentiate glucose-induced insulin secretion	• Antioxidant • Antiapoptotic • Antiinflammatory • Antihyperglycemic
3	Genistein	• Soya beans • Fava beans • Chickpeas	• Increase β-cell mass • Improves glucose tolerance • Reduce apoptosis	• Antioxidant • Antihyperglycemic
4	Hesperidin	• Oranges • Lemons	• Increase serum insulin • Decrease glucose and HbA1C	• Antiinflammatory • Antioxidant • Antihyperglycemic
5	Rutin	• Buckwheat • Asparagus • Apple	• Improves oxidative stress • Decrease serum glucose	• Antioxidant • Antihyperglycemic • Neuroprotective
6	Carotenoid (Lycopene)	• Pink grapefruit • Tomatoes	• Decrease lipid peroxidation • Increased activity of antioxidant enzymes	• Antioxidant • Antihyperglycemic

Bioactive Compounds Against EDCs Induced Hypertension

Amaranth oil has an effect on biomarkers of hypertension and result in reduction of LDL, cholesterol, and triglycerides [55]. This change in composition is conducted by replacing saturated fats with unsaturated fats. Cocoa enriched with polyphenols also possesses blood pressure lowering activity [56, 57]. The polyphenols in cocoa are responsible for endothelial function, platelet inhibition, and thus reduction in blood pressure through nitric oxide signaling [58, 59]. The improved endothelium function produces a reduction in blood pressure especially caused by polyphenols in dark chocolate. Administration of potassium supplementation reduces blood pressure in potassium deficient hypertensive patients. Stimulation of Na^+/K^+ATPase in smooth muscles and adrenergic nerve terminals triggers vasodilation, therefore, potassium is considered as an effective mediator of increased blood pressure [60–62]. Lycopene found in tomatoes are effective in management of hypertension. Lycopene is an antioxidant which inactivates free radicals, improving endothelium function and reducing low density lipoproteins susceptibility to oxidation [60]. Vitamin C or Ascorbic acid also plays role in reduction of blood pressure through improved endothelial function carried out by scavenging free radicals within vasculatures [59]. However, combination of vitamin C with antihypertensive amlodipine gives more favorable result than amlodipine itself [63]. Vitamin E found in spinach, almonds, and sunflower seeds also possesses antihypertensive property through increase in intracellular magnesium level [64]. The lower blood pressure may be due to the magnesium induced diarrhea and hypovolemia. It also enhances diuretic effect by restoring potassium and magnesium in body [54]. Table 28.2 describes the summary of sources, proposed mechanisms of action, and therapeutic properties of various bioactive compounds used in hypertension.

Effect of Bioactive Compounds Against EDC's Induced Obesity

Abnormal or excessive fat accumulation characterized by body mass index of greater or equal to 30 kg/m^2 is termed as Obesity [65]. There are certain chemicals called obesogens that disrupt normal metabolism after entering the body. The connection between hormones and receptors is blocked by endocrine disrupting chemicals. EDCs result in changing the sensitivity to glucose and metabolism of lipids. These changes predispose a person to gain weight [66].

Bioactive Compounds for Treatment of EDCs Induced Obesity

There are numerous bioactive compounds proved to be effective measures for the management of EDCs induced obesity.

Table 28.2 Effect of bioactive compounds against EDCs induced hypertension

Sr. #	Bioactive compounds	Source	Mechanism of action	Therapeutic property
1	Cocoa	• Dark chocolate	• Reduce blood pressure through nitric oxide signaling	• Antihypertensive
2	Lycopene	• Tomatoes	• Improve endothelium function • Inactivate free radicals	• Antioxidant • Antihypertensive
3	Vitamin C	• Citrus fruit	• Improve endothelium function trough scavenging free radicals	• Antihypertensive
4	Vitamin E	• Spinach • Almonds • Sunflower seeds	• Increase intracellular magnesium level which enhance diuretic action	• Antihypertensive

Fiber

Both insoluble (hemicellulose, cellulose, and lignin) and soluble (inulin, psyllium, beta-glucans, pectins) fibers reduce cholesterol and sugar levels in blood [67]. Prebiotic fibers enhance fat and glucose metabolism after breakdown into short-chain fatty acids [68].

Monounsaturated Fats and Polyunsaturated Fats (Omega-3 and Omega-6)

Plant sterols, monounsaturated and polyunsaturated fats, and essential fatty acids are effective in increasing high density lipoproteins and decreasing total cholesterols instead of saturated fats and trans-fatty acids [69].

Vitamin C and Vitamin E

The consumption of Vitamin C and Vitamin E decreases lipid peroxidation and proinflammatory cytokines and thus reduces the risks of vascular disease. Inadequate Vitamin C contributes to an elevation of circulating lipopolysaccharides due to overgrowth of intestinal bacteria [70].

Bioactive Peptides

Bioactive peptides scavenge free radicals and reduce cholesterol and regulate blood pressure. During ripening process of cheese, concentration of strong antihypertensive agent such as lactotripeptides increases. These bioactive peptides also result in appetite suppression in case of obesity [71].

Minerals

Several minerals have demonstrated potential role in the management of obesity. Calcium intake of (1200 mg/day) increases fat mass loss in obese and overweight adults [72]. Low calcium intake results in decreased lipolysis which in turn increases weight [73].

Phytochemicals

Bioactive compounds such as triterpenes and carotenoids, and phytochemicals primarily polyphenols (flavonoid, flavonols, flavones, anthocyanins, phenolic acids, stilbenes, and curcuminoids) exhibit significant antiadiposity, antioxidative, and cardioprotective [74–78]. Some phytochemicals act as thermogenic compounds (ephedrine, caffeine, salicylic acid, and capsaicin) and prevent accumulation of fat in body tissues through burning extra calories [72].

Probiotics

Microorganisms that maintain the balance of intestinal flora in gut and improve digestibility of nutrients are termed probiotics. Probiotics belong to genera Lactobacillus and Bifidobacterium. Gut microbiota are found to be effective in treatment of obesity. Apparently, intestinal microflora lead to increased energy storage and adiposity in obese than that of lean individuals [79]. Moreover, short-chain fatty acids (acetate, butyrate, and propionate) from indigestible polysaccharides are produced by beneficial intestinal microflora which may act as energy substrates as well as regulators of food intake and satiety. Lactobacilli and Bifidobacteria synthesize bioactive isomers of conjugated linoleic acid which possess antidiabetic, antiatherosclerotic and anti obesity properties [80]. Table 28.3 describes the summary of sources, proposed mechanisms of action, and therapeutic properties of various bioactive compounds used in obesity.

Effect of Bioactive Compounds Against EDCs Induced Hyperlipidemia

Hyperlipidemia is a metabolic disorder characterized by high cholesterol or elevated levels of fats in the blood. EDCs interfere with synthesis, secretion, and release of hormones. Therefore, hyperlipidemia is caused by even low dose exposure to BPA due to upregulation of genes involved in cholesterol synthesis including sterol regulating element binding protein 2 [81].

Table 28.3 Bioactive compounds against EDC's induced obesity

Sr. #	Bioactive compounds	Source	Mechanism of action	Therapeutic property
1.	Fiber	• Citrus fruit • Oatmeal • Barley • Apple	Enhance fat and glucose metabolism	• Anti- obesity agent
2.	Omega 3 and Omega 6	• Fish • Flaxseed • Soyabeans • Vegetable oil • Corn	Reduce plasma triglycerides	• Anti-obesity agent
3.	Vitamin C and Vitamin E	• Citrus fruit • Almonds • Peanuts • Sunflower	Decrease lipid peroxidation and proinflammatory cytokines	• Anti-obesity agent • Antiinflammatory
4.	Bioactive peptides	• Egg • Fish • Meat	Scavenge free radicals and reduce cholesterol	• Anti-obesity agent • Antioxidant
5.	Minerals	• Milk • Green vegetables • Cashew nuts	Increase lipolysis	• Anti-obesity agent
6.	Phytochemicals	• Vegetables • Grains • Fruit	Prevent accumulation of fats through burning extra calories	• Anti-obesity agent
7.	Probiotics	• Milk • Yogurt	Inhibition of α-amylase and pancreatic lipase activity	• Anti-obesity agent

Bioactive Compounds Against EDCs Induced Hyperlipidemia

Black mulberry has demonstrate positive results for the treatment of hypercholesterolemia, obesity, and diabetes [82]. Phenolics compounds in black mulberry possess antioxidant property [83–85]. Berberine is a bioactive compound found in berberries which downregulate genes involved in synthesis of lipids.

Effect of Bioactive Compounds Against EDCs Induced NAFLD

Non-alcoholic fatty liver disease (NAFLD) includes a spectrum of liver disorders ranging from steatosis to non-alcoholic steato-hepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma. EDCs have gained special attention for their ability to impair hepatic function. Plasticizers (bisphenol A), persistent organic pollutants (dioxins), organotins (tributyltin), organochlorines (dichlorodiphenyltrichloroethane) are examples of some EDCs that might cause NAFLD through peripheral

effects of obesity on adipose dysfunction, liver cell autonomous effects, and deregulation of satiety axis in hypothalamus. EDCs challenge homeostasis and lead to several pathological processes including metabolic disorders, oxidative stress, and inflammation. These processes result in imbalance, leading to the development of steatosis and NASH. NASH may progress to fibrosis and cirrhosis. Flavonoid protects against NAFLD by decreasing radicals formation, cytokines production, and increasing antioxidant enzymes [86].

Bioactive Compounds Against EDCs Induced NAFLD

Natural compounds such as flavonoids, carotenoids, and polyphenols found in our routine diet demonstrate beneficial effects attributing to their antioxidants, antiinflammatory and metabolic activities (Fig. 28.2).

Coumestrol

Coumestrol is a natural organic compound found in brussels sprout, spinach, clover, legumes, and soya beans [87]. Coumestrol increases fatty acid oxidation in myocytes and decreases the mRNA expression of lipogenic genes in hepatocytes [88].

Anthocyanins

Water soluble pigments of colored berries, vegetables, and fruits are basically anthocyanidins. They provide protection to hepatocytes injury by improving antioxidant status and inhibiting mitochondria pathways of apoptosis [89].

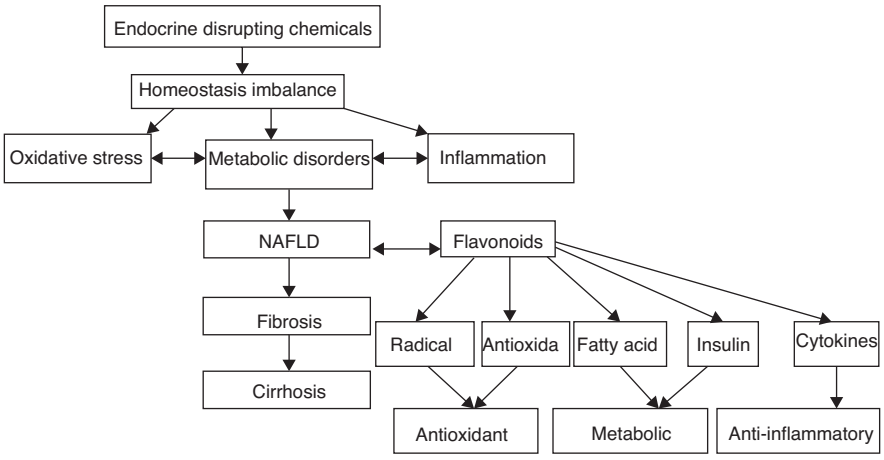

Fig. 28.2 Pathogenesis of EDCs induced NAFLD

Curcumin

Curcumin is a polyphenol obtained from rhizome of curcuma longa. It possesses antioxidant, antiinflammatory, and antimutagenic properties. Curcumin reduces oxidative stress by inhibiting aconitase (oxidative stress marker) [90]. It also reduces lipogenesis by facilitating β-oxidation [18].

Astaxanthin

Astaxanthin is a carotenoid found in crayfish, shrimp, yeast, and salmon. Astaxanthin provides protection against fatty liver disease by reducing lipid peroxidation and lipid accumulation in liver. It also downregulates genes involved in lipogenesis [91].

Green Tea Flavonoids

Green tea flavonoids include epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate [92–94]. However, flavonoids comprise small amounts of quercetin and myricetin that are found to be effective in treatment of NAFLD. Quercetin improves lipid metabolism through stimulation of fatty acid oxidation and inhibition of lipogenesis. Quercetin exerts antioxidant effects demonstrated by reduction of oxidative stress. Therefore, administration of quercetin led to decrease in steatosis. Citrus fruit such as oranges and grapefruit contain rutin (Quercetin with disaccharides rutinose covalently bound to 3-OH groups) [94]. Few studies reported beneficial effect of rutin in NAFLD through reduction of oxidative stress and stimulation of endogenous antioxidants level [95]. Table 28.4 describes the summary of sources, proposed mechanisms of action, and therapeutic properties of various bioactive compounds used in NAFLD.

Conclusions and Recommendations

Bioactive compounds possess promising ability to interact with living tissues by presenting one or more probable health benefits. Research related to the use of bioactive compounds in EDCs induced metabolic disorders is experiencing remarkable growth. More specific information on bioactive compounds consumption and human health will be forthcoming in future. Increased consumption of bioactive rich food including vegetables, fruits and grains protects against metabolic disorders. The mechanism of action involves antioxidant, antiinflammatory, antimutagenic, and antiapoptotic properties.

Conflict of Interest The authors have no affiliations or involvement in any organization or entity with any financial interest.

Table 28.4 Bioactive compounds against EDC's induced NAFLD

	Bioactive compounds	Source	Mechanism of action	Therapeutic property
1	Coumestrol	• Brussels sprouts • Clover • Legumes • Spinach • Soya beans	Decrease mRNA expression of lipogenic genes in hepatocytes	• Antioxidant
2	Anthocyanins	• Berries • Vegetables • Fruits	Improve antioxidant status and inhibiting mitochondrial pathways of apoptosis	• Antioxidant
3	Curcumin	• Curcuma longa	Reduces lipogenesis by facilitating β-oxidation	• Antioxidant • Antiinflammatory • Antimutagenic
4	Astaxanthin	• Crayfish • Shrimp • Salmon • Yeast	Reduces lipid peroxidation and lipid accumulation in liver	• Antioxidant
5	Flavonoids	• Green tea	Stimulation of fatty acids oxidation and inhibition of lipogenesis	• Antioxidant

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Correction to: Endocrine Disrupting Chemicals-induced Metabolic Disorders and Treatment Strategies

Muhammad Sajid Hamid Akash, Kanwal Rehman, and Muhammad Zaffar Hashmi

Correction to:
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The original version of this book was inadvertently published with an incorrect affiliation (Al-Jouf University) of the authors Tauqeer Hussain Mallhi, Yusra Habib Khan, Abdulaziz Ibrahim Alzarea, and Nasser Hadal Alotaibi. All these authors were the contributors of Chapters 6, 10, and 28.

The correct affiliation "Jouf University" has been updated in all the affected chapters.

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