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.

References

1. Monneret C. What is an endocrine disruptor? C R Biol. 2017;340(9-10):403–5.
2. Rhomberg LR, Goodma JE, Foster WG, Borgert CJ, Van-Der KG. A critique of the European Commission document, “State of the Art Assessment of Endocrine Disrupters”. Crit Rev Toxicol. 2012;42(6):465–73.

3. Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, et al. Endocrine-disrupting chemicals: an endocrine society scientific statement. Endocr Rev. 2009;30(4):293–342.
4. Rousselle C, Ormsby JN, Schaefer B, Lampen A, Platzek T, Hirsch-Ernst K, et al. Meeting report: international workshop on endocrine disruptors: exposure and potential impact on consumers health. Regul Toxicol Pharmacol. 2013;65(1):7–11.
5. Casals-Casas C, Desvergne B. Endocrine disruptors: from endocrine to metabolic disruption. Annu Rev Physiol. 2011;73:135–62.
6. Colborn T, Vom Saal FS, Soto AM. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. Environ Health Perspect. 1993;101(5):378–84.
7. De Coster S, Van Larebeke N. Endocrine-disrupting chemicals: associated disorders and mechanisms of action. J Environ Public Health. 2012;2012:713696.
8. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of comorbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health. 2009;9(1):88.
9. Keith SW, Redden DT, Katzmarzyk PT, Boggiano MM, Hanlon EC, Benca RM, et al. Putative contributors to the secular increase in obesity: exploring the roads less traveled. Int J Obes (Lond). 2006;30(11):1585–94.
10. Hamilton MT, Hamilton DG, Zderic TW. Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease. Diabetes. 2007; 56(11):2655–67.
11. Smith MS. H. Maurice Goodman: Basic medical endocrinology. 4th ed. Cambridge: Academic Press; 2009.
12. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab. 2004; 89(6):2548–56.
13. Newbold RR, Padilla-Banks E, Jefferson WN. Environmental estrogens and obesity. Mol Cell Endocrinol. 2009;304(1-2):84–9.
14. Howdeshell KL, Hotchkiss AK, Thayer KA. Vandenbergh JG, vom Saal FS. Exposure to bisphenol A advances puberty Nature. 1999;401(6755):763–4.
15. Newbold RR, Padilla-Banks E, Snyder RJ, Jefferson WN. Developmental exposure to estrogenic compounds and obesity. Birth Defects Res A Clin Mol Teratol. 2005;73(7):478–80.
16. Grün F, Blumberg B. Endocrine disrupters as obesogens. Mol Cell Endocrinol. 2009; 304(1-2):19–29.
17. Evans RM, Barish GD, Wang YX. PPARs and the complex journey to obesity. Nat Med. 2004;10(4):355–61.
18. Hurst CH, Waxman DJ. Activation of PPARα and PPARγ by environmental phthalate monoesters. Toxicol Sci. 2003;74(2):297–308.
19. Rubin BS, Soto AM. Bisphenol A: perinatal exposure and body weight. Mol Cell Endocrinol. 2009;304(1-2):55–62.
20. Gore AC. Endocrine-disrupting chemicals. JAMA Intern Med. 2016;176(11):1705–6.
21. Neel BA, Sargis RM. The paradox of progress: environmental disruption of metabolism and the diabetes epidemic. Diabetes. 2011;60(7):1838–48.
22. Nadal A, Fuentes E, Ripoll C, Villar-Pazos S, Castellano-Muñoz M, Soriano S, et al. Extranuclear-initiated estrogenic actions of endocrine disrupting chemicals: Is there toxicology beyond paracelsus? J Steroid Biochem Mol Biol. 2018;176:16–22.
23. Longnecker MP, Daniels JL. Environmental contaminants as etiologic factors for diabetes. Environ Health Perspect. 2001;109(suppl 6):871–6.
24. Yang O, Kim HL, Weon JI, Seo YR. Endocrine-disrupting chemicals: review of toxicological mechanisms using molecular pathway analysis. J Cancer Prev. 2015;20(1):12–24.
25. Spanogiannopoulos P, Bess EN, Carmody RN, Turnbaugh PJ. The microbial pharmacists within us: a metagenomic view of xenobiotic metabolism. Nat Rev Microbiol. 2016;14(5):273–87.
26. Patterson AD, Turnbaugh PJ. Microbial determinants of biochemical individuality and their impact on toxicology and pharmacology. Cell Metab. 2014;20(5):761–8.

27. Carmody RN, Turnbaugh PJ. Host-microbial interactions in the metabolism of therapeutic and diet-derived xenobiotics. J Clin Invest. 2014;124(10):4173–81.
28. Donovan SM. Introduction to the special focus issue on the impact of diet on gut microbiota composition and function and future opportunities for nutritional modulation of the gut microbiome to improve human health. Gut Microbes. 2017;8(2):75–81.
29. Forslund K, Hildebrand F, Nielsen T, Falony G, Le Chatelier E, Sunagawa S, et al. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. Nature. 2015;528(7581):262–6.
30. Claus SP, Guillou H, Ellero-Simatos S. The gut microbiota: a major player in the toxicity of environmental pollutants? NPJ Biofilms Microbiomes. 2016;2:16003.
31. Snedeker SM, Hay AG. Do interactions between gut ecology and environmental chemicals contribute to obesity and diabetes? Environ Health Perspect. 2011;120(3):332–9.
32. Van de Wiele T, Gallawa CM, Kubachk KM, Creed JT, Basta N, Dayton EA, et al. Arsenic metabolism by human gut microbiota upon in vitro digestion of contaminated soils. Environ Health Perspect. 2010;118(7):1004–9.
33. Lu K, Abo RP, Schlieper KA, Graffam ME, Levine S, Wishnok JS, et al. Arsenic exposure perturbs the gut microbiome and its metabolic profile in mice: an integrated metagenomics and metabolomics analysis. Environ Health Perspect. 2014;122(3):284–91.
34. Zhang S, Jin Y, Zeng Z, Liu Z, Fu Z. Subchronic exposure of mice to cadmium perturbs their hepatic energy metabolism and gut microbiome. Chem Res Toxicol. 2015;28(10):2000–9.
35. Ba Q, Li M, Chen P, Huang C, Duan X, Lu L, et al. Sex-dependent effects of cadmium exposure in early life on gut microbiota and fat accumulation in mice. Environ Health Perspect. 2017;125(3):437–46.
36. Wu J, Wen XW, Faulk C, Boehnke K, Zhang H, Dolinoy DC, et al. Perinatal lead exposure alters gut microbiota composition and results in sex-specific bodyweight increases in adult mice. Toxicol Sci. 2016;151(2):324–33.
37. Zhang Y, Zhao F, Deng Y, Zhao Y, Ren H. Metagenomic and metabolomic analysis of the toxic effects of trichloroacetamide-induced gut microbiome and urine metabolome perturbations in mice. J Proteome Res. 2015;14(4):1752–61.
38. Lai KP, Chung YT, Li R, Wan HT, Wong CC. Bisphenol A alters gut microbiome: comparative metagenomics analysis. Environ Pollut. 2016;218:923–30.
39. Taylor KW, Novak RF, Anderson HA, Birnbaum LS, Blystone C, DeVito M, et al. Evaluation of the association between persistent organic pollutants (POPs) and diabetes in epidemiological studies: a national toxicology program workshop review. Environ Health Perspect. 2013;121(7):774–83.
40. Lambert JE, Myslicki JP, Bomhof MR, Belke DD, Shearer J, Reimer RA. Exercise training modifies gut microbiota in normal and diabetic mice. Appl Physiol Nutr Metab. 2015; 40(7):749–52.
41. Chen L, Zhang W, Hua J, Hu C, Lok-Shun Lai N, Qian PY, et al. Dysregulation of intestinal health by environmental pollutants: involvement of the estrogen receptor and aryl hydrocarbon receptor. Environ Sci Technol. 2018;52(4):2323–30.
42. Xun L, Topp E, Orser C. Glutathione is the reducing agent for the reductive dehalogenation of tetrachloro-p-hydroquinone by extracts from a Flavobacterium sp. Biochem Biophys Res Commun. 1992;182(1):361–6.
43. James-Todd TM, Huang T, Seely EW, Saxena AR. The association between phthalates and metabolic syndrome: the National Health and Nutrition Examination Survey 2001–2010. Environ Health Perspect. 2016;15(1):52.
44. James-Todd T, Stahlhut R, Meeker JD, Powell SG, Hauser R, Huang T, et al. Urinary phthalate metabolite concentrations and diabetes among women in the National Health and Nutrition Examination Survey (NHANES) 2001–2008. Environ Health Perspect. 2012;120(9):1307–13.
45. Hu J, Raikhel V, Gopalakrishnan K, Fernandez-Hernandez H, Lambertini L, Manservisi F, et al. Effect of postnatal low-dose exposure to environmental chemicals on the gut microbiome in a rodent model. Microbiome. 2016;4(1):26.

46. Provvisiero D, Pivonello C, Muscogiuri G, Negri M, de Angelis C, Simeoli C, et al. Influence of bisphenol A on type 2 diabetes mellitus. Int J Environ Res Public Health. 2016;13(10):989.
47. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. 2012;490(7418):55.
48. Greiner T, Bäckhed F. Effects of the gut microbiota on obesity and glucose homeostasis. Trends Endocrinol Metab. 2011;22(4):117–23.
49. Alonso-Magdalena P, Vieira E, Soriano S, Menes L, Burks D, Quesada I, et al. Bisphenol A exposure during pregnancy disrupts glucose homeostasis in mothers and adult male offspring. Environ Health Perspect. 2010;118(9):1243–50.
50. Montgomery MP, Kamel F, Saldana TM, Alavanja MCR, Sandler DP. Incident diabetes and pesticide exposure among licensed pesticide applicators: Agricultural Health Study, 1993–2003. Am J Epidemiol. 2008;167(10):1235–46.
51. Jaacks LM, Staimez LR. Association of persistent organic pollutants and non-persistent pesticides with diabetes and diabetes-related health outcomes in Asia: A systematic review. Environ Int. 2015;76:57–70.
52. Velmurugan G, Ramprasath T, Swaminathan K, Mithieux G, Rajendhran J, Dhivakar M, et al. Gut microbial degradation of organophosphate insecticides-induces glucose intolerance via gluconeogenesis. Genome Biol. 2017;18(1):8.
53. Swaminathan K, Veerasekar G, Kuppusamy S, Sundaresan M, Velmurugan G, Palaniswami NG. Noncommunicable disease in rural India: Are we seriously underestimating the risk? The Nallampatti noncommunicable disease study. Indian J Endocrinol Metab. 2017;21(1):90–5.
54. Harishankar MK, Sasikala C, Ramya M. Efficiency of the intestinal bacteria in the degradation of the toxic pesticide, chlorpyrifos. 3 Biotech. 2013;3(2):137–42.