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Oestrogens, adipose tissues and environmental exposures influence obesity and diabetes across the lifecycle

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Endogenous oestrogens regulate essential functions to include menstrual cycles, energy balance, adipose tissue distribution, pancreatic β-cell function, insulin sensitivity and lipid homeostasis. Oestrogens are a family of hormones which include oestradiol (E2), oestrone (E1) and oestriol (E3). Oestrogens function by binding and activating oestrogen receptors (ERs). Phytoestrogens are plant-derived compounds which exhibit oestrogenic-like activity and can bind to ERs. Phytoestrogens exert potential oestrogenic-like benefits; however, their effects are context-dependent and require cautious consideration regarding generalised health benefits. Xenoestrogens are synthetic compounds which have been determined to disrupt endocrine function through binding to ERs. Xenoestrogens enter the body through various routes and given their chemical structure they can accumulate, posing long-term health risks. Xenoestrogens interfere with endogenous oestrogens and their functions contributing to conditions like cancer, infertility, and metabolic disorders. Understanding the interplay between endogenous and exogenous oestrogens is critical in order to determine their potential health consequences and requires further investigation. This manuscript provides a summary of the role endogenous oestrogens have in regulating metabolic functions. Additionally, we discuss the impact phytoestrogens and synthetic xenoestrogens have on biological systems across various life stages. We highlight their mechanisms of action, potential benefits, risks and discuss the need for further research to bridge gaps in understanding and mitigate exposure-related health risks.

Key words: Estrogen: Phytoestrogen: Xenoestrogen: Obesity: Diabetes

Overview

Functions of endogenous oestrogens

Sex steroids, including testosterone and oestrogens, are present in both males and females, and their biological functions and production undergoes changes across the life cycle. We will focus our article on the role of oestrogens in mediating metabolic functions. In females, certain oestrogens surge during puberty and pregnancy but decline during menopause. Oestrogens are pivotal for growth, development, sexual differentiation and reproduction. Oestrogens have diverse roles throughout the body, and they regulate functions to include menstrual cycles[(1)], energy balance[(2)], adipose tissue distribution

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and well-being[3,4], pancreatic β-cell function and viability[5], skeletal muscle insulin sensitivity[6], liver lipid balance[7] and macrophage function and polarisation[8]. Importantly, any disruption to the function of oestrogens can potentially lead to conditions such as obesity[9], adipose tissue inflammation[4], atherosclerosis[10], changes in adipose tissue distribution and function[4], pancreatic β-cell dysfunction[11,12], fatty liver[13], impaired peripheral tissue glucose regulation[14] and systemic inflammation[15]. The goal of this review is to explore how natural oestrogens affect metabolic function and discuss how plant-based and artificial oestrogens also impact metabolism across the life cycle. We conclude by emphasising the need for further research to fill knowledge gaps.

Endogenous oestrogens

Endogenous oestrogens – a 'family' of oestrogens. Oestrogens are a cohort of sex steroid hormones derived from cholesterol. Among the endogenous physiological oestrogens, three primary forms exist: oestrone (E1), oestradiol (E2) and oestriol (E3). E2 holds prominence as the primary oestrogenic compound circulating during a woman's reproductive years, and it remains dominant until menopause. Following menopause, E1 gains significance as a key oestrogenic compound, while E3 assumes a major role during pregnancy, even though it's considered the least potent oestrogen[16].

The synthesis of oestrogens in ovarian granulosa cells hinges on the activation of an enzyme named aromatase (CYP19A1), which belongs to the cytochrome P450 superfamily. This enzyme facilitates the aromatisation process, wherein androgens, particularly testosterone and androstenedione, are transformed into oestradiol and oestrone. Notably, studies on animals lacking this enzyme have revealed an inability to produce oestrogens[17,18]. In women during their reproductive years, the ovaries, corpus luteum and placenta serve as primary sites for oestrogen production. Additionally, smaller amounts of oestrogens are synthesised by non-gonadal organs such as the liver, heart, skin, brain, adipose tissues, intestines and adrenal glands[19]. In prepubescent females and males, oestrogens are produced in non-gonadal locations, where their functional effects are typically exerted locally through paracrine and/or intracrine mechanisms[16].

Following the onset of menopause, adipose tissue stromal cells and preadipocytes exhibit high expression levels of aromatase, 17b-hydroxysteroid dehydrogenases (17bHSD) and CYP1B1. Among these, 17bHSD plays a role in converting weak androgens and/or oestrogens into their more potent counterparts to include the conversion of androstenedione into testosterone and oestrone into oestradiol[20]. Due to the substantial mass of adipose tissue, its contribution to whole-body steroid metabolism is notably significant.

E2 levels in humans and rodents. In pre-menopausal individuals, the levels of E2, or oestradiol, exhibit a range of 15–400 pg/ml, a variance largely contingent on the phase of the menstrual cycle. Conversely, E2 levels plummet to less than 10 pg/ml during menopause. Rodents have been used to study and learn more about the physiological functions of oestrogens. Rodents undergo a reproductive cycle, termed the oestrous cycle, divided into four distinct phases—proestrus, oestrus, metestrus and diestrus—spanning about 4–5 d. Throughout this cycle, the concentration of circulating E2 within rodents displays significant fluctuations. Among these phases, proestrus showcases the highest E2 concentration, roughly ranging between 30–60 pg/ml. Even during diestrus and metestrus, E2 remains detectable with the use of sensitive instrumentation, albeit at levels not surpassing 5 pg/ml. Remarkably, during the oestrus stage, E2 has been found to be undetectable[21–24].

Oestrogens modulate homeostasis through binding and activation of oestrogen receptors. Oestrogens exert their effects through the mediation of oestrogen receptors (ERs), which comprise nuclear receptors, surface membrane receptors, and are found in various forms such as ERα (ESR1), ERβ (ESR2), G protein-coupled receptors (GRP30 and Gq-mER) and ER-X. Nuclear ERs function as transcription factors, overseeing the modulation of specific gene transcription. On the other hand, surface membrane ERs, once activated by oestrogens, instigate rapid intracellular signalling pathways[16]. Beyond their interaction with ERs, oestrogens can also regulate enzymatic activities and engage with non-steroid-hormone-nuclear receptors, consequently initiating signalling pathways that are independent of ERs[16].

Effects of endogenous oestrogens on obesity, diabetes and the metabolic syndrome. Many women exhibit features of the metabolic syndrome (abdominal adiposity, insulin resistance and dyslipidemia) with the onset of oestrogen deficiency at menopause. There are direct effects of oestrogen deficiency on body fat distribution, insulin action, effect on arterial wall and fibrinolysis that may contribute to an increased prevalence of the metabolic syndrome in post-menopausal women compared to pre-menopausal women[25]. Fabre et al., postulated that membrane-initiated ERα extra-nuclear signalling contributes to female, but not to male, protection against high-fat-diet-induced obesity and associated metabolic disorders in mouse[26].

Exogenous oestrogens

Exogenous oestrogens obtained through the diet. Oestrogens can also be introduced into the body from external sources, either through the consumption of certain foods or exposure to various environmental factors. These exogenous oestrogen exposures are capable of exhibiting oestrogen-like activities, which involve binding to ERs and other nuclear hormone receptors. There are two distinct categories of exogenous oestrogens: xenoestrogens, which are synthetic oestrogens, and phytoestrogens, which are phytochemicals derived naturally from plants. Phytoestrogens possess the potential to exert both beneficial effects and

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function as endocrine disruptors[27]. The roles and effects of phytoestrogens will be explored in greater detail further below. Xenoestrogens also bind to and activate ERs and currently data suggests these exert endocrine disruption and may have long-term negative effects as will also be discussed below.

Phytoestrogens

Phytoestrogens, compounds resembling oestrogens and sourced from plants, are commonly found in soy products, grains, peas, beans, as well as in specific fruits and vegetables[28,29]. Phytoestrogens can be classified into three main categories based on their chemical structures: (1) Flavonoids, such as genistein, daidzein, glycitein and biochanin, and they are frequently present in soy products and are often marketed as dietary supplements; (2) Coumestans, represented by compounds like coumestrol, wedelolactone and plicadin, can be found in foods like broccoli and sprouts, with their oestrogenic activity significantly surpassing that of isoflavones; (3) Lignans, originate from plant cell walls and are polyphenolic components present in plants, seeds, whole grains and certain vegetables. This category also encompasses compounds like enterodiol, enterolactone, pinoresinol, matairesinol and sesamin, some of which are produced by intestinal bacteria and exert relatively mild oestrogenic effects[28–30].

Phytoestrogens have the ability to bind to and activate oestrogen receptors. Phytoestrogens exhibit the ability to bind to and activate ERs. Interestingly, data suggest phytoestrogens demonstrate a preference for oestrogen receptor beta activation (ERβ), as evidenced by the ratios of binding affinity of these compounds relative to binding to ERα *v.* ERβ: Genistein $\beta/\alpha = 20$, Daidzein $\beta/\alpha = 7$, S-Equol $\beta/\alpha = 32$, Coumestrol $\beta/\alpha = 7$, Naringenin $\beta/\alpha = 11$, Apigenin $\beta/\alpha = 20$[31,32]. Moreover, phytoestrogens are known to also bind to serotonergic receptors and insulin-like growth factor receptors exerting biological effects which are impacted by the duration and age for which exposure has occurred. Phytoestrogens possess the capability to enhance the binding of free radicals and can directly or indirectly influence the activation of tyrosine kinases, cyclic adenosine monophosphate pathways, phosphatidylinositol-3 kinase (PI3K), DNA methylation, as well as histone and RNA expression[28].

Detrimental or beneficial phytoestrogen function(s)? The discussion surrounding whether phytoestrogens yield positive or negative effects is ongoing. Crucially, it is important to recognise that the timing, type, duration and level of exposure plays pivotal roles in determining whether these oestrogenic compounds offer advantages or pose risks. Moreover, the context matters significantly as to whether phytoestrogens are therapeutic for conditions like alleviating menopausal symptoms, reducing osteoporosis, or potentially exerting anti-tumorigenic properties. When low endogenous levels of oestrogens exist, there are data suggesting phytoestrogenic benefits; however, the potential for off-target or side effects post-consumption/exposure remains less understood[33]. Moreover, when phytoestrogens are consumed in combination with drugs, phytoestrogens can interfere with the drug efficacy and function, implying that additional data and caution may be necessary to ascertain if phytoestrogen intake affects the safety of other medications. It is worth noting that the beneficial effects of phytoestrogens could differ in pre-menopausal women with higher endogenous oestrogen levels[33] when compared to post-menopausal women. Additionally, the impact of phytoestrogens on men, who naturally have lower circulating levels of oestrogens, is also less understood.

The timing of phytoestrogen exposure emerges as a critical factor influencing their potential positive or negative effects. Exposure can occur during foetal development, adulthood, in the presence or absence of endogenous oestrogens, and in both females and males. However, establishing an association between dietary phytoestrogens and endocrine biomarkers remains inconclusive, partly due to variations in the type and concentration of compounds, the bioavailability of phytoestrogens, and whether they affect circulating *v.* urinary excretion of metabolites[33,34].

Xenoestrogens

Xenoestrogens are compounds which mimic oestrogenic functions and are not produced within the body. Xenoestrogens are synthetic in origin and include chemicals used as solvents/lubricants. Xenoestrogens, like phytoestrogens, are structurally and functionally similar to oestrogens and they bind to the ERs producing biological effects some of which might be beneficial; however, in most cases they have been shown to be detrimental. In fact, xenoestrogens and their byproducts such as plastics like bisphenol A (BPA), plasticisers (phthalates), pesticides (DDT), pharmaceutical agents, are considered to be environmental hazards due to their hormone-disruptive effects[27] and xenoestrogens are classified as endocrine disrupting chemicals (EDCs) because they: '*interfere with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for development, behaviour, fertility and maintenance of homeostasis*'[35].

Xenoestrogens enter the body through various routes, including ingestion and absorption from foods, exposure to dust and water, inhalation of airborne gases and particles, and direct contact with the skin[36]. Moreover, they can be transmitted to developing foetuses through maternal transfer and to infants via breast milk or formula prepared with water containing xenoestrogens. Once inside the body, xenoestrogens engage with endogenous oestrogens and oestrogen receptors (both membrane and nuclear receptors), leading to disruption of oestrogenic signalling[37–39].

Xenoestrogens, akin to other endocrine disrupting substances (EDCs), can interfere with the synthesis, secretion, transport, metabolism, binding, action, or elimination of oestrogens[40,41]. Their relatively low water solubility and high lipid solubility contribute to a lengthy

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environmental half-life. Additionally, due to their chemical makeup, xenoestrogens are widely distributed in the environment and tend to accumulate in wastewater, consequently impacting marine animal reproduction[42].

Among the most hazardous classes of xenoestrogens is bisphenol-A (BPA). BPA is extensively used in the production of plastics, thermal paper, can linings and dental sealants[43]. Exposure to BPA has been associated with various hormone-related cancers[44]. Moreover, data suggest that BPA can interfere with neuronal development, leading to physiological and behavioural effects[45]. Another perilous group is halogenated bisphenols A (H-BPAs), including tetrachlorobisphenol A (TCBPA). These compounds are employed in manufacturing and present in different environmental contexts, demonstrating greater toxicity than BPA[46]. Diethylstilbestrol (DES), another xenoestrogen, was administered to women from the 1940s to the 1970s to lower the risk of miscarriages[36,47–49]; tragically, it resulted in birth defects and has since been banned.

BPA enhances the pathogenesis processes of type 2 diabetes mellitus which includes insulin resistance, impaired glucagon secretion and pancreatic β-cell dysfunction[50–52]. BPA accelerates the cellular senescence and apoptosis by increasing the metabolic stress of high glucose[53]. BPA exposure is also associated with promoting disturbances in lipid metabolism and insulin resistance[54]. Many studies in the past were able to identify a possible link between the BPA-induced organ damage mechanisms and pathogenesis of diabetic complications[55,56].

Xenoestrogen's 'estrogen-like' activity. Xenoestrogens not only engage with and activate ERs and oestrogen-related receptors, but they also interact with androgen receptors and retinoid receptors. Moreover, xenoestrogens can directly or indirectly bind to non-steroid receptors, including neurotransmitter receptors like serotonin, dopamine and norepinephrine receptors. They can also interact with orphan receptors, such as the aryl hydrocarbon receptor (AhR), triggering enzymatic pathways that influence steroid biosynthesis and metabolism[56]. Many xenoestrogens possess a phenolic structure resembling that of E2, allowing them to interact with ERs as either agonists or antagonists[57]. Their binding affinities for ERs span from sub-nanomolar to micromolar values, and once bound, they can function as full agonists or partial agonists/antagonists[42]. Xenoestrogens can also serve as hormone precursors, thereby impacting steroid metabolism and functioning as steroid-sensitive substrates[58]. However, the relationship between BPA and metabolic outcomes is complicated by a non-monotonic dose response curve. Various epidemiological studies assumed a linear relationship between BPA exposure and diabetes risk but lately it has been postulated by the regulatory agencies that BPA can mitigate adverse effects at much lower doses than the calculated safe dose[59,60].

Xenoestrogens may negatively influence various health conditions, including breast and prostate cancer, endometriosis, infertility, diabetes, metabolic syndrome, early puberty and obesity. Xenoestrogens can interfere with the development of the female reproductive tract by competitively inhibiting endogenous oestrogens and selectively binding to ERs. Specific substances, such as nine PCBs, three pesticides, a furan, and two phthalates, have been linked to gradual damage to the follicular pool and associated with earlier onset of menopause[61]. Xenoestrogens can also contribute to the formation of ovarian cysts, leading to a condition known as polycystic ovary syndrome[62]. Adolescents residing in areas with significant industrial development and PCB exposure experienced earlier menarche and thelarche compared to their unexposed peers[63]. A National Health and Nutrition Examination study showed higher BPA exposure is associated with obesity in the adult population of the United States[64]. Riffee et al., explored the relationship between bisphenol exposure and lipid profile parameters and exercise-induced glucose uptake mechanisms and indicated that BPA and bisphenol S are highly correlated with oxidative stress generation and impaired lipid metabolism[65].

Foetal development. Xenoestrogens have been demonstrated to provide detrimental effects on foetal development, with evidence indicating negative impacts on neuronal and endocrine function[66]. These compounds have also been associated with cancer-promoting mutations within cells during foetal development[67]. Furthermore, exposure to xenoestrogens during pregnancy has been linked to alterations in the genetic sequence within the placenta, thereby adversely affecting foetal growth and overall development[68,69]. A study by Garcia-Arvelo et al., exposed mice to BPA subcutaneously and fed a high-fat diet and the authors found the male offspring had fasting hyperglycaemia, glucose intolerance and high levels of NEFA in the plasma compared with the controls[69]. An epigenomic-wide analysis of cord blood DNA methylation indicated that there may be sex specific epigenomic responses to BPA exposure in offspring as well[70].

The term used to define the timing for which an individual is exposed to xenoestrogens is referred to as the 'term window'[40]. Determining the 'term window' is extremely challenging and yet may be critical in determining if and when the impact of the exposure is manifested and to what harm the organism may experience due to the exposure. The 'term window' is the period of developmental susceptibility during which the developing organism can be altered by environmental factors resulting in structural, functional and/or cellular changes[40].

Limitations and gaps in knowledge

Two recent Scientific Statements from The Endocrine Society have highlighted the urgent necessity to delve into the fundamental mechanisms of action xenoestrogens exert and the subsequent physiological impacts of endocrine disruptors they impart[40,41]. It cannot be understated that there is of utmost importance to conduct

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foundational *in vitro* molecular investigations to uncover the pathways through which xenoestrogens exert their influence on endocrine tissues[40,41].

How to minimise exposure. Given the documented adverse effects of xenoestrogen exposure, one effective strategy to minimise risk is to reduce the use of cosmetic products that contain parabens and phthalates. Additionally, using glass or ceramic containers for storing food, as opposed to plastic, is recommended due to the heightened presence of xenoestrogens in plastics. It's advisable to avoid using plastic containers in the microwave to prevent potential leaching of BPA into microwaved products. Additionally, refraining from heating plastics, even in direct sunlight, is recommended to mitigate exposure[71,72].

Moreover, adjusting dietary consumption of foods which contain high levels of xenoestrogens can aid in decreasing exposure. Specifically, restricting the intake of canned fish which can contain elevated levels of mercury and PCBs, would be prudent[73,74]. Health professionals and nutrition experts advocate for consumption of fresh fish which is high in *n*-3 long-chain PUFA[75,76]. Additionally, various studies indicate that consuming fish might protect against the effects of methyl mercury[77–79]. For instance, research conducted in the Seychelles Child Development Study suggests a positive correlation between fish consumption and cognition[78,79]. Moreover, opting for pesticide-free fruits and vegetables is advisable whenever possible. If this is not feasible, then ensuring that fruit and vegetables are washed thoroughly prior to consumption could minimise exposure[80–82].

Inability to conduct research on xenoestrogens

Research on xenoestrogens is constrained by ethical considerations because conducting studies to explore the harmful effects of these substances on humans can pose moral challenges. Many studies available in the literature are observational or conducted on animals, thereby limiting the direct applicability of their findings to humans. The scarcity of randomised controlled trials in the realm of xenoestrogen exploration is notable. As previously indicated, potential detrimental effects of xenoestrogens occur as they accumulate within organisms and are contingent on factors such as dosage and exposure duration, which may not be discernible within shorter timeframes. A deeper understanding necessitates further experiments involving the examination of the impact of xenoestrogens both in their environmental context and in isolation.

Conclusion

Oestrogens exert many critical functions throughout the body. Endogenous oestrogens, particularly oestradiol, have vital roles in growth, development and reproduction. Additionally, oestrogens function beyond reproduction and include regulating energy balance, adipose tissue distribution and insulin sensitivity. Because of the vital biological function oestrogens have, exposure to exogenous oestrogens, like phytoestrogens from plants and synthetic xenoestrogens, can have profound effects which may be both beneficial and harmful.

Phytoestrogens, found in foods, can bind to oestrogen receptors, potentially offering benefits for various conditions. However, their effects depend on timing and exposure levels, raising questions about safety and interactions with medications. Xenoestrogens on the other hand, are synthetic compounds derived from various sources and they mimic oestrogens and can disrupt endocrine function, affecting health outcomes, including cancer and reproductive disorders. Avoiding certain products containing xenoestrogens and making dietary choices can help reduce exposure risks.

Clearly understanding the impact xenoestrogens have on biological systems is critical yet research on xenoestrogens faces ethical and complexity challenges, limiting our understanding. Many studies are observational or conducted in animal models which do not completely replicate human physiological function therefore requiring further investigation to bridge gaps between animal and human responses. Variability in doses and exposure durations underscores the need for more extensive experiments to comprehend their impacts accurately. Understanding the interplay between endogenous and exogenous oestrogens is crucial for health. Ongoing research guided by ethical considerations is essential to unravel complexities, inform strategies to minimise exposures and mitigate potential health risks.

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Conflict of interest

No conflicts of interest for any of the authors.

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